# British Journal of UROLOGY

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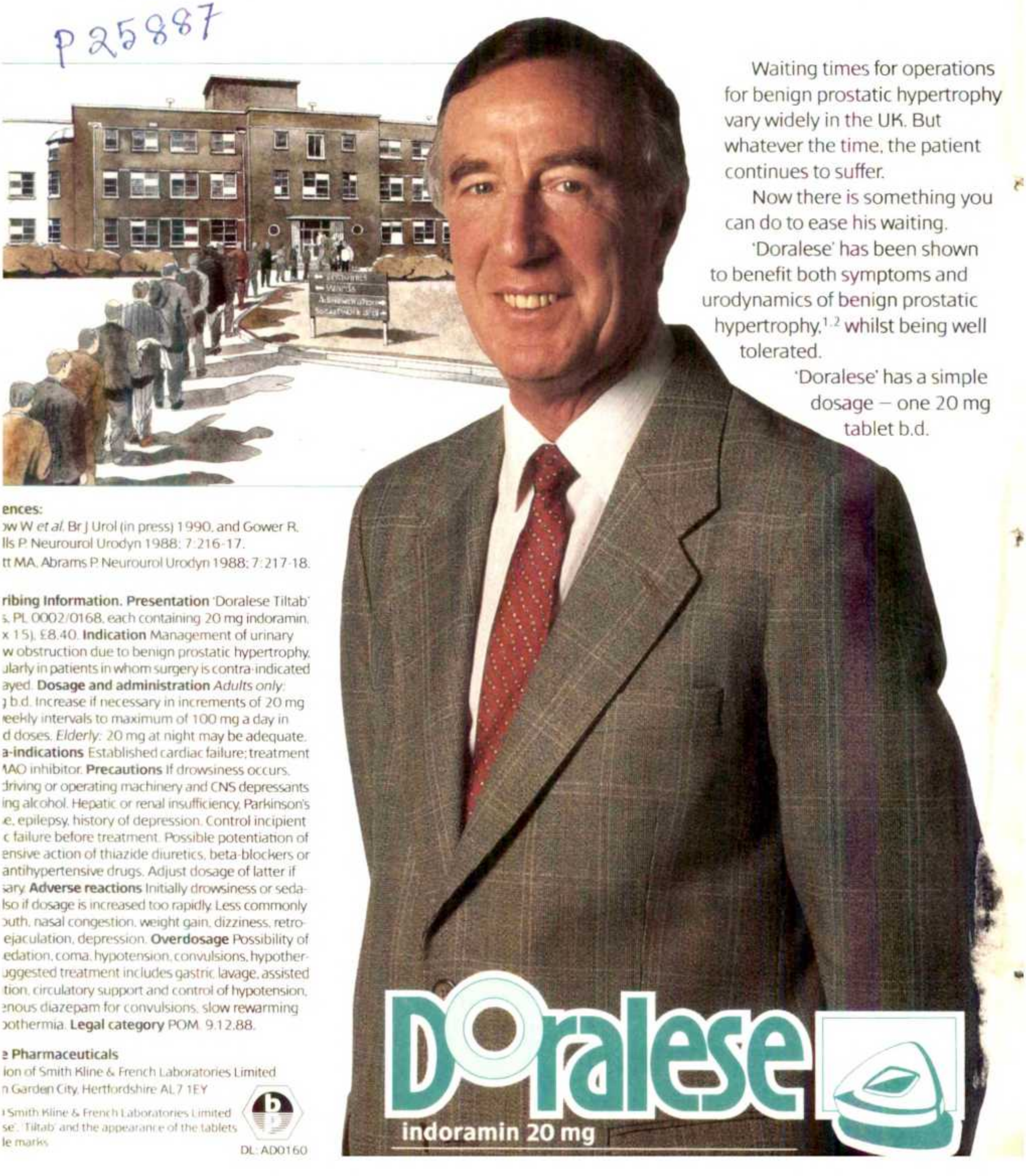

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ɔw W *et al.* Br J Urol (in press) 1990, and Gower R.
lls P. Neurourol Urodyn 1988; 7:216-17.
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lso if dosage is increased too rapidly. Less commonly
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REVIEW

# Role of Diagnostic Imaging in the Evaluation and Treatment of Post-operative Complications of the Urinary Tract

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Often physicians are reluctant to publish details of their surgical complications and as a result it is difficult to assess accurately from the literature the frequency of complications related to particular procedures. Nevertheless, there is an apparent increase in the incidence and variety of urinary tract complications being described now that more elderly and debilitated patients are undergoing surgical, endourological and percutaneous procedures.

Iatrogenic injuries to the urinary tract are not uncommon. While gynaecological surgery is responsible for over 52% of iatrogenic ureteric injuries, the actual risk of injury to the ureter during pelvic surgery is low, with an estimated incidence of 0.4 to 1.5% (Dowling *et al.*, 1986; Daly and Higgins, 1988). Radical hysterectomies present the greatest risk, with surgical injury to the ureter occurring in 10 to 30% (Dowling *et al.*, 1986). In addition, a variety of new endourological and percutaneous procedures, many of which are still in their infancy and being performed by inexperienced physicians, increase the potential for urinary tract damage.

Regardless of the aetiology of damage to the urinary tract, appropriate management decisions are contingent on an accurate diagnosis and assessment of the injury. Complications may be recognised in the peri-operative period or present at a variable time subsequently. Often the diagnosis of urinary tract injury may be delayed as a result of non-specific presenting symptoms, such as abdominal discomfort, nausea and fevers. Specific complications may be attributable to the unique anatomy, function and pathophysiology of the urinary tract (Table 1). An understanding of the many types of post-surgical complications in the urinary tract may help the astute physician to circumvent unwarranted outcomes.

More importantly, when suspicion of a possible complication arises, requesting the appropriate diagnostic tests is essential. Initial delineation of the urinary tract anatomy, frequently modified by surgical procedures, is essential for accurate assessment of urological complications. A search for abnormal fluid collections and urinary tract leakage, obstruction and fistula is required. Cross-sectional imaging with computed tomography (CT) and ultrasound (US) provides accurate delineation of the urinary tract and permits diagnosis of most post-operative complications. More specific structural detail of the urinary tract frequently requires a contrast examination such as intravenous urography, loopography or antegrade pyelography.

The radiologist can not only aid the urologist and the general surgeon by establishing the diagnosis, but may provide therapeutic options as definitive therapy or as an adjunct to surgery. Radiological interventional techniques may enable definitive non-operative treatment of many patients or, alternatively, provides a temporising measure, particularly in situations where distorted anatomy, poor tissue healing and generally deteriorating clinical state are present.

## I. Diagnostic Imaging Modalities

Diverse diagnostic imaging techniques are available for assessing normal and abnormal urinary tract

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**Table 1** Post-Operative Urological Complications

- I. Obstruction caused by:
  - Post-operative distortion and oedema
  - Hydronephrosis
  - Extrinsic compression by fluid collection or haematoma
  - Accidental ligation of ureter
  - Ureteroceles, pseudoureteroceles
  - Stricture
  - Calculus—pre-existing or newly formed
  - Extrinsic encasement by spread or recurrence of tumour
- II Leakage due to:
  - Perforation
  - Dehiscence
  - Erosion
  - Ureteric avulsion
  - Extrusion of calculi
- III. Fluid collection—possible aetiologies:
  - Haematoma
  - Urinoma
  - Seroma
  - Abscess
  - Lymphocele
- IV. Fistula—ureteric communication to:
  - Cutaneous
  - Enteric
  - Vaginal
  - Arterial
  - Lymphatic
- V. Bleeding
  - Into the kidney or collecting system
  - Perirenal or retroperitoneal
  - Arteriovenous fistulas and malformations
- VI. Renal artery obstruction caused by:
  - Embolus or thrombus
  - Pseudoaneurysm
  - Stenosis in renal transplant
- VIII. Miscellaneous
  - Retained foreign bodies
    - ureteric stent, balloon catheter

anatomy and function (Table 2). These include intravenous urography, ultrasound, retrograde and antegrade pyelograms, nuclear medicine, CT, magnetic resonance imaging (MRI) and angiography. A comparison of some of the advantages and disadvantages of these tests for diagnosing post-operative complications is shown in Table 2. Which technique to use will be influenced by the stability of the patient, the surgical procedure performed, the presenting level of renal function, the possibility of infection and local prejudices and biases. Evaluation of post-operative urinary tract complications requires a logical approach to address the clinical situation and the degree of suspicion for a particular complication. The appropriate imaging modality to be used should be tailored to each case. Although some recommendations are made in this review, an absolute imaging algorithm cannot be provided.

## II. Therapeutic Interventional Techniques

Interventional uroradiological and vascular procedures are well established clinically (Table 3). These techniques are an important alternative to surgical intervention, for they avoid re-operation in unstable patients with distorted anatomy and compromised tissue healing. Hospitalisation is frequently reduced and out-patient management often possible. These techniques may provide definitive treatment or may serve as an adjunct to formal surgical intervention, preserving renal function while providing time for improvement in the patient's general condition and healing of the operative site. Palliative therapy may be possible for otherwise inoperable patients.

A brief description of the types of interventional techniques is presented below. However, the uroradiological interventions to be used in particular situations need to be suited to each individual patient; a discussion of the correct application of these tests for particular complications follows.

### *Percutaneous nephrostomy*

Placement of a percutaneous nephrostomy was first introduced in 1955 for drainage of an obstructed urinary tract (Goodwin *et al.*, 1955). Nephrostomy diversion is performed in order to preserve renal function in an obstructed collecting system and is also used in the treatment of sepsis aggravated or caused by ureteric obstruction (Lang and Price, 1983). More recently, nephrostomy placement is a first step prior to interventional techniques aimed at dissolving or basketing renal calculi, dilatation of ureteric strictures and placement of antegrade stents (Fritzsche, 1986; Lang and Glorioso, 1988).

### *Stents*

The first reported cases of cannulation of the ureter during open cystostomy date back to the nineteenth century (Saltzman, 1988). Little advance occurred until the last 2 decades, during which time a virtual explosion in research and development has been directed toward refinement in stent characteristics, indications and functions. Ureteric stents are now routinely used as an adjunct to open surgery of the urinary tract. Accurate stent placement is crucial to preserve the anastomosis from vascular compromise, urinary leakage with periureteric fibrosis, infection or kinking (Mitty *et al.*, 1983; Saltzman, 1988). Percutaneous or endoscopic placement of

**Table 2** Comparison of Diagnostic Imaging Examinations of the Urinary Tract

| *Examination* | *Image mechanism* | *Invasiveness* | *Advantages* | *Disadvantages* | *Diagnostic ability* |
|---|---|---|---|---|---|
| Intravenous urography (IVU) | Radiation (external beam) | Venopuncture<br>Requires intravenous contrast medium | Delineates anatomy of collecting system<br>Gross determinant of renal function<br>Easy to perform<br>Widely available | Contrast reactions<br>Requires adequate renal function | Hydronephrosis<br>Obstruction<br>Leaks/fistulas |
| Ultrasound | Sound waves | None | Rapid<br>Readily available | Unable to determine physiology<br>Operator-dependent | Hydronephrosis<br>Fluid collections |
| Computed tomography (CT) | Radiation (external beam) | None, unless intravenous contrast is administered | Excellent anatomical detail including all of the surrounding abdomen and retroperiteum | Not always available | Hydronephrosis<br>Obstruction<br>Fluid collections<br>Adjacent masses<br>Leaks/fistulas |
| Radionuclide renography | Radiation (internal beam) | Yes<br>Requires injection of radioactive isotope | Evaluates renal function | Poor anatomical definition | Obstruction<br>Leakage |
| Magnetic resonance imaging (MRI) | Magnetic field | None | Excellent anatomical detail of pelvic structures | Expensive<br>Little experience with diagnostic use for urinary tract | Hydronephrosis<br>Fluid collections<br>Adjacent masses |
| Antegrade pyelography | Radiation (external beam) | Yes<br>Insertion of a needle into the collecting system | Good anatomical detail of collecting system | Risk of pain, bleeding or infection | Obstruction<br>Leaks/fistulas<br>Urodynamic testing |

stents is also advocated for ureteric strictures, leaks and fistulas, caused by a myriad of benign and malignant processes (Saltzman, 1988).

### *Dilatation*

Dilatation of the ureter may be accomplished by various techniques, including simple stenting with a catheter, the use of progressively larger catheters, a coaxial system and balloon dilatation (Fritzsche, 1986). An antegrade approach via a percutaneous nephrostomy tract with balloon catheters is now the preferred procedure for stricture dilatation (Johnson *et al.*, 1987). Recent post-operative strictures appear most amenable to dilatation. Older, more densely fibrotic strictures and those secondary to ischaemia and malignancy are often refractory to dilatation (Lang, 1986).

### *Percutaneous lithotripsy and basketing*

Access to the collecting system via the nephrostomy site permits instrumentation for grasping and fragmenting calculi. Snares, graspers, forceps and helical baskets have all been used successfully to remove calculi and other foreign bodies such as retained catheter parts. Nephroscopes and lithotripsy devices are also readily manipulated into the collecting system to visualise, pulverise and extract calculi.

### *Needle localisation, aspiration, drainage and biopsy*

With the development of cross-sectional imaging, solid and cystic masses in the retroperitoneum, abdomen and pelvis are easily detected by US and CT. In the past, post-surgical fluid collections often remained undetected until complicating factors such as sepsis or urinary tract obstruction demanded re-exploration of the patient. Today, fine needle aspiration of fluid masses under CT or US guidance with biochemical analysis and culture will usually establish the precise diagnosis. Aspiration and drainage may be the only treatment required in most cases, obviating surgery.

### *Vascular interventions*

Transcatheter vessel occlusion in the kidney is effective for a variety of conditions including tumour, haemorrhage and arteriovenous communications (McLean and Meranze, 1986). Bleeding originating from within the kidney can enter the renal collecting system, resulting in haematuria, or instead, may enter the retroperitoneum and produce a perirenal or pararenal haematoma. Renal hae-

**Table 3** Indications for Interventional Radiological Techniques

| *Interventional radiological procedures* | *Urological complications potentially treated* | *Comments* |
|---|---|---|
| TRANSRENAL PROCEDURES | | |
| Percutaneous nephrostomy | Decompression of urinary obstruction<br>Urinary diversion<br>Stone dissolution<br>Chemotherapy<br>Urodynamic assessment (Whitaker testing)<br>Access for: Nephrolithomy<br>Foreign body retrieval<br>Laser therapy<br>Nephroscopy | Renal function is preserved by diverting urine flow from any ureteric obstruction or leakage<br>The nephrostomy tract also provides access to the collecting system for further diagnostic evaluation and therapeutic intervention |
| Antegrade ureteric stenting | Ureteric strictures<br>Ureteric leaks or dehiscence<br>Ureteric fistulas<br>Extrinsic tumour compression | Stents maintain ureteric lumen patency and divert urine flow from ureteric defects |
| Ureteric stricture dilatation | Benign ureteric strictures<br>Pelvic junction strictures<br>Malignant strictures | Dilatation obviates the need for surgery in patients with benign obstruction and in patients with malignant disease who may not tolerate major surgery |
| Balloon occlusion of the ureter | Uncontrollable fistulas and leaks | Achieves permanent urinary blockade above a ureteric leak without surgical intervention |
| PERCUTANEOUS PROCEDURES | | |
| Aspiration and drainage of fluid collections | Urinoma<br>Haematoma<br>Abscess<br>Seroma<br>Lymphocele | Percutaneous aspiration achieves rapid diagnostic sampling of fluid and provides access for drainage |
| Fine needle biopsy | Tumour<br>Fibrosis | Percutaneous biopsy rapidly distinguishes benign from malignant aetiologies |
| Ureteric clips | Uncontrollable fistulas and leaks | Permanent urinary blockade provided above a ureteric leak |
| VASCULAR PROCEDURES | | |
| Embolisation | Haemorrhage<br>Tumour necrosis | Rapidly achieves control of bleeding or serves to decrease arterial supply to tumour masses |
| Transluminal angioplasty | Arterial stenosis in renal transplants<br>Arterial stenosis following bypass grafts | Restoration of arterial flow without surgical intervention |
| Intra-arterial fibrinolysis | Renal artery thrombosis following bypass grafts or angioplasty | Restoration of arterial flow without surgical intervention |

morrhage can occur following renal biopsy, percutaneous nephrostolithotomy or percutaneous nephrostomy placement.

Transcatheter renal arterial embolisation is an established form of treatment for gross haematuria. If the renal capsule is ruptured, bleeding into the retroperitoneum can be massive. Embolisation of significant renal bleeding can be accomplished with the balloon occlusion catheter positioned selectively in the artery supplying the ruptured segment. Various kinds of embolic material have been described for focal arterial bleeding. When used to treat neoplastic diseases, successful embolisation of the arteries supplying a tumour mass results in tissue ischaemia and necrosis.

Those patients who develop renal insufficiency as a result of renal artery stenosis may benefit from renal artery angioplasty to stabilise or improve residual renal function.

## Post-operative Urological Complications

### *Obstruction*

The mechanisms for upper urinary tract obstruction are numerous. Regardless of the aetiology, the development of increased collecting system pressure damages the renal parenchyma (Kerr, 1954; Wilson, 1980).

The incidence of post-operative obstruction varies with the type of surgical procedure performed. Transient renal obstruction is attributed to post-operative oedema at the suture line, to blood clot, to pelvic outlet obstruction from a nephrostomy tube or to intestinal ileus (Johnston *et al.*, 1977; Hendren *et al.*, 1980; Sullivan *et al.*, 1980). Hendren *et al.* (1980) claimed that delayed opening of the anastomosis was the most common post-operative complication following pyeloplasty. Transient obstruction also occurs after extracorporeal shock wave lithotripsy (ESWL); ureteric "colic" of less than 24 hours' duration is common following ESWL and occurred in 30% of the 1252 kidneys treated by Kellum *et al* (1987). Surgical procedures not directly related to the urinary tract, such as aortic bypass grafting, can also cause transient hydronephrosis in the early post-operative period (Goldenberg *et al.*, 1988).

Conservative management with close follow-up often suffices for patients with early post-operative hydronephrosis. Renal ultrasonography and computed radionuclide urography will help to determine the presence of obstruction and the relative degree of remaining renal function (Lang and Glorioso, 1988; Gottlieb *et al.*, 1989). Antegrade pyelography and Whitaker testing, if necessary, will confirm ureteric lumen patency or the level of any obstruction. Figure 1 shows a recommended algorithm in the management of post-operative obstruction.

Anastomotic leakage of urine, bleeding outside the collecting system, abscess collections and lymphoceles may cause extrinsic compression on the ureter, thereby obstructing urine flow. Suture ligation, retained stones and incorrect positioning of ureteric stents can all cause partial or complete obstruction. Ultrasonography may determine the presence of hydronephrosis but cannot always establish the existence of obstruction. Alternatively, urography and CT with contrast are superior in establishing the presence of obstruction and specifying the site and the aetiology of the obstruction.

Impacted calculus fragments following ESWL may cause incomplete distal ureteric obstruction. A column of calculus debris in the mid and distal portions of the ureter (Steinstrasse) and bulbous configuration of the ureter on urography establish an unequivocal diagnosis (Kellum *et al.*, 1987; Barber *et al.*, 1988). Such an observation requires follow-up with radionuclide scintigraphy or intravenous urography to exclude impaired renal function as a result of the obstruction. Placement of a percutaneous nephrostomy tube will relieve the obstruction and permit irrigation of residual debris.

Ureteric obstruction may also develop secondary to stricture formation. Regardless of aetiology, the pathophysiology of stricture formation is presumably secondary to compromised vascular supply (Lang, 1986). In benign conditions, devascularisation occurs from calculus disease, fulminating inflammation and prior surgery or trauma (Lang, 1986). Anastomotic leakage of urine or bleeding can precipitate periureteric and retroperitoneal fibrosis (Lang, 1986; Saltzman, 1988; Spirnak *et al.*, 1989). Encroachment of neoplastic tissue, surgical stripping of the ureter to debulk tumour mass and radiation therapy to the abdomen can cause extensive cicatricial fibrosis compromising ureteric vascularity and lumen patency (Lang, 1986; Saltzman, 1988).

The diagnosis of a suspected stricutre is best confirmed by opacification of the ureteric lumen (Fig. 2). Intravenous urography and antegrade or retrograde pyelography can delineate the extent of any abnormalities within the collecting system. Direct access to the ureter may be obtained in an antegrade or a retrograde manner or by direct surgical insertion of a T-tube (Gordon *et al.*, 1986). Through any of these routes, further diagnostic and interventional uroradiological techniques can be performed.

The success of balloon dilatation of strictures appears directly related to the duration, length and aetiology of the stricture (Beckmann *et al.*, 1989). When performed on fresh strictures of less than 3 months' duration, dilatation has a success rate of up to 91% (Lang and Glorioso, 1988; Beckmann *et al.*, 1989). In studies reviewing all types of ureteric stricture dilatation, the overall sucess rate ranges from 58 to 76% (Johnson *et al.*, 1987; Beckmann *et al.*, 1989). Older strictures (duration 3 months or more) are more refractory to dilatation, most likely as a result of progressive fibrotic reaction compromising vascular supply (Lang, 1986; Lang and Glorioso, 1988). Similarly, strictures arising from cicatricial changes, inflammatory responses and devitalisation following surgery or radiation are the least responsive (Lang, 1986). In long-term follow-up of 51 patients with evidence of strictures with ischaemic compromise, Lang and Glorioso (1988) achieved only a 20% success rate. Therefore, long segments of stenosed or devitalised ureter with strictures usually benefit from antegrade or retrograde stenting (Lang, 1986; Saltzman, 1988).

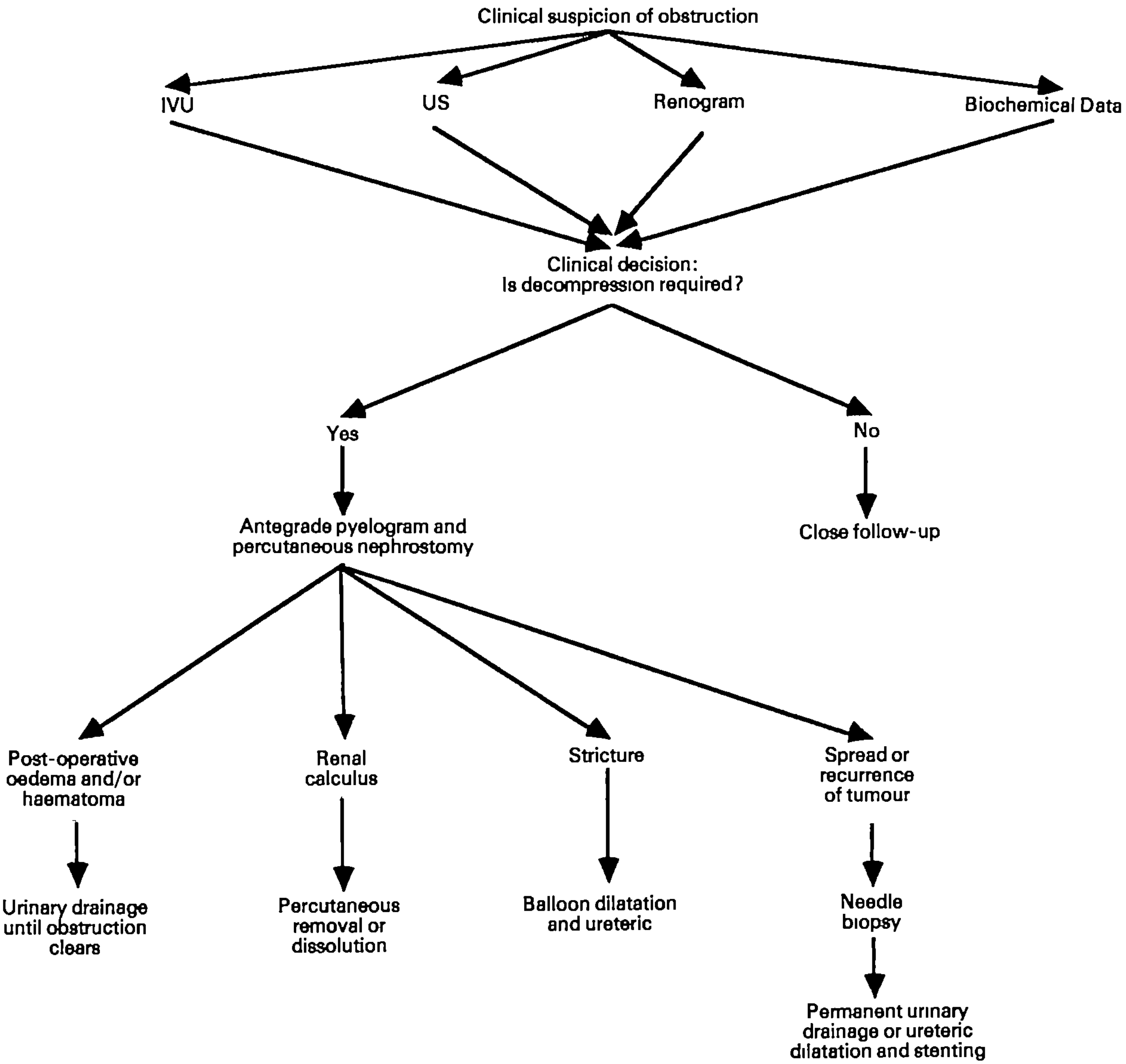
Clinical suspicion of obstruction
IVU
US
Renogram
Biochemical Data
Clinical decision:
Is decompression required?
Yes
No
Antegrade pyelogram and percutaneous nephrostomy
Close follow-up
Post-operative oedema and/or haematoma
Renal calculus
Stricture
Spread or recurrence of tumour
Urinary drainage until obstruction clears
Percutaneous removal or dissolution
Balloon dilatation and ureteric
Needle biopsy
Permanent urinary drainage or ureteric dilatation and stenting

Fig. 1 Approach to post-operative urinary tract obstruction

Similarly, ureteric encasement or invasion by neoplastic tissue is usually refractory to dilatation and may require permanent stenting. Regardless of aetiology, most strictures merit an attempt at balloon dilatation followed by temporary stenting.

At present, percutaneous transluminal dilatation has become the procedure of choice for treatment of most benign ureteric strictures (Lang, 1986). Ureteroscopic pyelolysis without percutaneous access (endopyelotomy) achieves similarly excellent results in relieving pelviureteric junction (PUJ) stricture (Badlani *et al.*, 1988 Weiss *et al.*, 1988).

When patency of the ureteric lumen cannot be established following the diagnosis of obstruction, placement of a percutaneous nephrostomy tube is an important measure to safeguard renal function by diverting the urine flow and by alleviating the back pressure on the kidney due to the obstructed collecting system. Thus preservation of the renal unit by temporary decompression is achieved until the compromised ureter can be corrected. Placement of a percutaneous nephrostomy also provides access to the proximal urinary tract and facilitates antegrade pyelography, Whitaker testing, ureteric dilation, stenting and dissolution or removal of renal calculi (Lang and Price, 1983).

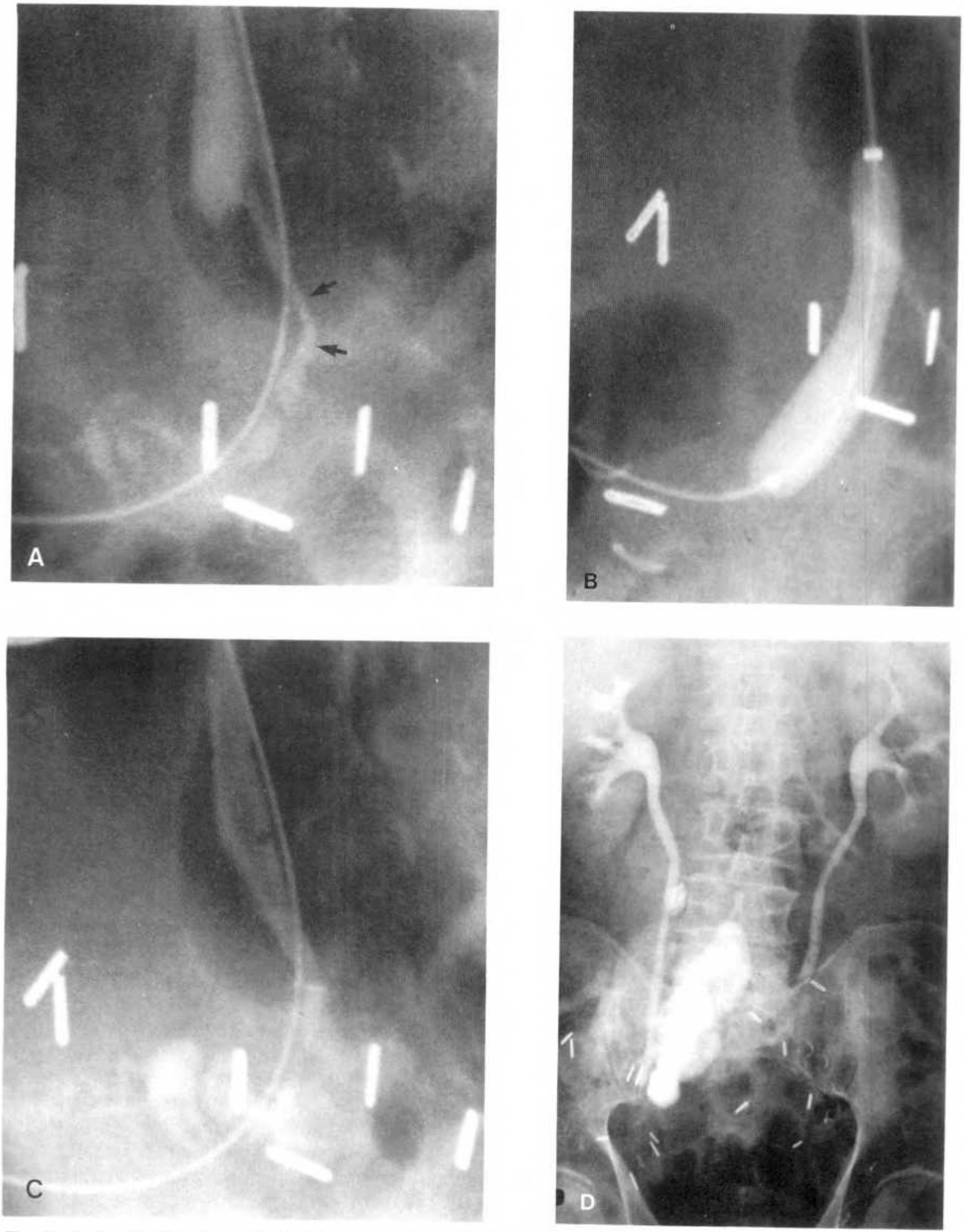

**Fig. 2** A 71-year-old man with ileal loop diversion following total cystectomy 2 years previously developed right-sided hydronephrosis. (A) A right percutaneous nephrostomy was performed and an antegrade urogram demonstrated a short uretero-ileal stricture (arrows). A guide wire was negotiated across the stricture. (B) A 10-mm diameter balloon catheter was inflated across the stricture site. (C) An antegrade urogram following balloon dilatation shows normal calibre of the uretero-ileal anastomosis. (D) Follow-up IVU at 1 year shows normal appearance of the right collecting system without recurrence of hydronephrosis.

### *Leakage*

Leakage of urine is not uncommon following major ureteric resection and reconstruction. During the first 4 days following pyeloplasty, urine leakage is routine; persistent leakage for more than 10 days is less frequent, however, with a reported incidence of 4.5% (Cromie, 1983). This incidence may range as high as 25% following uretero-ileal conduit surgery (Sullivan *et al.*, 1980). Tumour resection, node biopsies and radical pelvic surgery put the ureter at risk of laceration (either partial or complete). If the urine leak continues for more than a week after surgery, the chance of periureteric inflammation and fibrosis increases dramatically. When a persistent urinary leak is suspected, appropriate evaluation by ultrasound or CT should be conducted, looking for a fluid collection.

The likelihood of anastomotic disruption increases when surgical and endourological procedures are performed in the presence of infection. It has been shown that infected urine markedly accelerates the resorption of Dexon and chromic sutures. Thus, if the collecting system does not remain sterile peri-operatively, the potential for anastomotic leak or disruption of the suture line becomes significant (Cromie, 1983).

The numerous endourological techniques being performed also place the ureter at increased risk of perforation. Laceration of the renal pelvis and ureter are not infrequent complications of antegrade or retrograde instrumentation of the urinary tract. Ureteroscopy can perforate or even avulse the distal ureter from the bladder (Badlani *et al.*, 1988). Also, stents can migrate in either direction and perforate (Saltzman, 1988). Long-term stenting predisposes the ureter to perforation through pressure necrosis and erosion (Saltzman, 1988). Finally, during nephrolithotomy, the incidence of inadvertent perforation of the ureter is reportedly from 1 to 2% (Lee *et al.*, 1986; Lang, 1987).

Extrusion of stones or stone fragments from the collecting system or ureter into the perinephric tissues or periureteric tissues may occur during percutaneous extraction (Lee *et al.*, 1986; Lang, 1987). In the absence of infection, extrusion of a calculus through a urothelial tear may be conservatively managed by nephrostomy drainage; ureteric stenting is reasonable to prevent stricutre formation of perforated ureters.

Clinical suspicion of a urine leak must be present if the diagnosis is to be made promptly. The clinical symptoms may merely be vague abdominal distress, which is not uncommon following intra-abdominal surgery. Ultrasonography is a helpful and rapid method for depicting fluid collections. Alternatively, CT has the advantage of precisely locating the leak and its association with surrounding structures. Free extravasation of contrast from the collecting system during urography is pathognomonic. Placement of a nephrostomy tube is often sufficient to divert the flow of urine. Conversion of the nephrostomy to a nephroureteric stent improves drainage and helps to prevent stricture formation at the site of leakage. Although much concern has been expressed about converting a partial tear to a complete laceration during ureteric manipulation, this has not been substantiated.

### *Fluid collections*

The accumulation of chronically extravasated urine outside the urinary tract is defined as a urinoma or uriniferous pseudocyst. The extravasation of urine into the perirenal or periureteric tissues at a rate greater than that which can be absorbed by the lymphatic precipitates lipolysis of perirenal fat, fibroblastic hyperplasia of the renal fascia and formation of a fibrotic sac encapsulating the urine (Lang and Glorioso, 1986). Obstructive causes of urinoma include calculus, posterior urethral valves and suture ligation. One of the nonobstructive causes is injury to the collecting system from blunt or penetrating trauma, including surgery or urological instrumentation (Fig. 3). For example, percutaneous nephrolithotomies are associated with a 1 to 2% incidence of urinoma, and pyeloplasty has an incidence of approximately 2.6% (Hendren *et al.*, 1980; Lang, 1987).

In much the same manner as with urinomas, a gradual leak of blood can collect and develop into a haematoma. Blood can also potentiate periureteric fibrosis and stricture formation. The incidence of perirenal haematoma formation is difficult to ascertain since most are asymptomatic and resolve spontaneously. Rosenbaum *et al.* (1978) reported an 85% incidence of perirenal haematoma documented by CT scanning when ordered following all renal biopsies. All patients were asymptomatic except for 1 who experienced flank pain and a 10% decrease in haematocrit. A similar prospective study revealed a 13% incidence of perierenal haematoma following percutaneous nephrostomy placement (Cronan *et al.*, 1985).

Lymphoceles often remain asymptomatic yet may present clinically as ipsilateral leg oedema, pelvic mass, ureteric obstruction or hypertension. Incomplete ligation of the lymphatics during nephrectomy or radical pelvic resection presumably

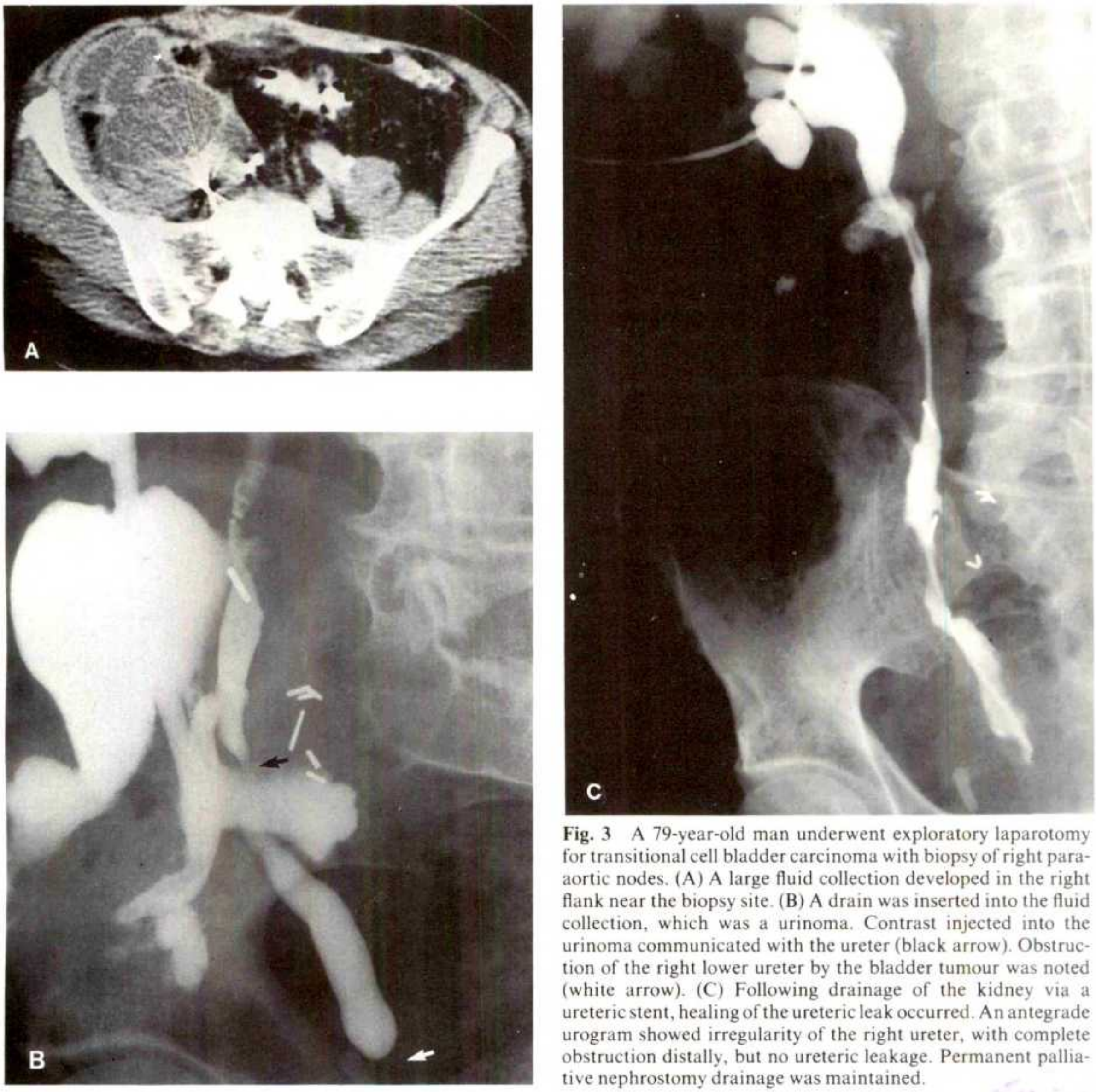

**Fig. 3** A 79-year-old man underwent exploratory laparotomy for transitional cell bladder carcinoma with biopsy of right para-aortic nodes. (A) A large fluid collection developed in the right flank near the biopsy site. (B) A drain was inserted into the fluid collection, which was a urinoma. Contrast injected into the urinoma communicated with the ureter (black arrow). Obstruction of the right lower ureter by the bladder tumour was noted (white arrow). (C) Following drainage of the kidney via a ureteric stent, healing of the ureteric leak occurred. An antegrade urogram showed irregularity of the right ureter, with complete obstruction distally, but no ureteric leakage. Permanent palliative nephrostomy drainage was maintained.

allows leakage and accumulation of lymph in the surrounding tissues. Lymphoceles usually develop 1 to 7 months after renal transplantation (Bennett *et al.*, 1986).

Static fluid, be it blood, urine or serosanguinous, which remains undrained may readily be seeded by micro-organisms and become a nidus for abscess formation. Early detection and appropriate intervention will avoid this unfortunate consequence.

The radiological diagnosis of these fluid collections may be suggested on intravenous urography by delayed or absent excretion of urine or displacement of the kidney or ureter by a mass. Extravasation of contrast from a functioning kidney would indicate leakage. Retrograde or antegrade pyelography would be required to demonstrate the anatomy of non-functioning kidneys. Ultrasonography would show a fluid collection or hydronephrosis if ureteric obstruction was present. CT scanning would depict the precise location of fluid collections in the retroperitoneal or intraperitoneal spaces and its relationship with other structures. Extravasation of contrast-enhanced urine can also be seen on CT. Fine needle aspiration is necessary

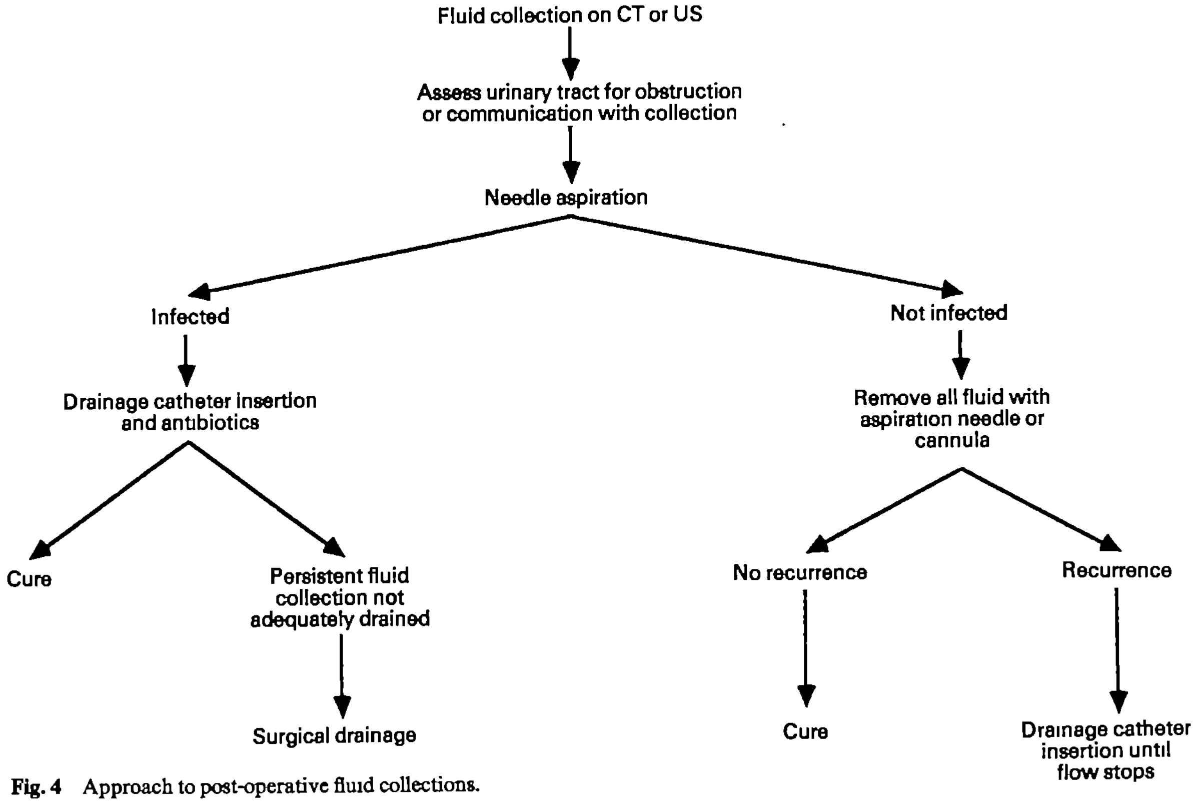
Fluid collection on CT or US
Assess urinary tract for obstruction or communication with collection
Needle aspiration
Infected
Not infected
Drainage catheter insertion and antibiotics
Remove all fluid with aspiration needle or cannula
Cure
Persistent fluid collection not adequately drained
No recurrence
Recurrence
Surgical drainage
Cure
Drainage catheter insertion until flow stops

**Fig. 4** Approach to post-operative fluid collections.

to define precisely the nature of these fluid collections and an approach to diagnosing and treating them is shown in Figure 4.

Uninfected fluid collections can be treated with simple aspiration but percutaneous catheter drainage is recommended for those that are infected. When a fistula to the ureter or lymphatics exists, longer drainage is necessary. Lymphoceles often require long-term drainage (2 to 7 months) and may ultimately need sclerosis with alcohol to precipitate obliteration. Abscesses usually respond in 5 to 8 days unless there is a communication with bowel or ureter, necessitating management of the fistula tract.

### *Fistula*

The diagnosis and management of urinary tract fistulas is complicated by the variety of fistulas and the complexity of clinical presentation. Fistulas may develop between the ureter and numerous structures including the skin, intestines, vagina and arteries (Lang, 1981; Darcy *et al.*, 1987). Surgery, ischaemia, recurrent tumour, chronic infection and previous radiation therapy all potentially jeopardise the ureter (Lang, 1981). Long-term indwelling ureteric stents may eventually produce pressure necrosis, erosion and fistula formation into neighbouring arteries (Saltzman, 1988).

Antegrade or retrograde pyelography will most often diagnose a direct communication between the ureter and a secondary structure. Direct injection into a cutaneous or vaginal tract may also delineate the source. Arteriography is required when brisk arterial bleeding is noted in the urine to delineate communication between the artery and the collecting system.

Primary surgical repair of urinary tract fistula fails in up to one-third of cases. When malignancy is the cause of the fistula, surgical closure is not advocated. Percutaneous nephrostomy tube placement and antegrade ureteric stenting are more successful than retrograde cystoscopic stent placement (Lang, 1981; Mitty *et al.*, 1983). Diversion of urine away from the fistula will often promote wound healing. Transrenal tamponade of the ureter with detachable or non-detachable balloons to achieve complete urinary diversion has met with limited success (Papanicolaou *et al.*, 1985; Gordon *et al.*, 1986). Some preliminary reports indicate that percutaneously applied ureteric clips may successfully treat intractable urinary fistulas with permanent and complete urinary diversion for symptomatic relief (Darcy *et al.*, 1987).

### *Bleeding*

As described previously, slow arterial bleeding can precipitate retroperitoneal and periureteric fibrosis and when this is suspected, cross-sectional imaging is recommended. Similarly, gross haematuria, especially in a patient with an indwelling ureteric stent, requires angiography to exclude an arterio-ureteric fistula.

Haemorrhage is often encountered during percutaneous nephrolithotomy and lithotripsy. In a multi-institution survey of 8595 procedures, Lang (1987) reported excessive bleeding ("red-out") that necessitated aborting the procedure in 68 patients (0.8%). Haemorrhage was listed as a "minor" complication in 231 cases (2.7%) and a "major" complication (*i.e.* required blood transfusion) in 37 (0.4%). Three of the 4 deaths in this large survey were attributable to uncontrollable haemorrhage. In other large series of patients undergoing percutaneous nephrolithotomy and lithotripsy, bleeding occurred in 3.5 to 12% of the cases (Lee *et al.*, 1986).

Arteriovenous fistula formation occurred in 39 (0.45%) of the percutaneous nephrolithotomies and lithotripsies described in Lang's survey and 26 of these required intervention (Lang, 1987). Haemorrhage requiring transfusion is also seen following endopyelotomy (Badlani *et al.*, 1988). Severe haematuria, pseudoaneurysms, arteriovenous malformations and expanding perirenal haematomas may develop from renal lacerations incurred during renal biopsy and percutaneous nephrostomy tube placement (Cronan *et al.*, 1985; McLean and Meranze, 1986).

Percutaneous transcatheter embolisation may be an effective way to obtain haemostasis when renal haemorrhage or haematuria occurs (McLean and Meranze, 1986). Precise angiographic characterisation of the site of extravasation of contrast or the anatomy of the fistula is required prior to attempting embolisation. A variety of techniques can be attempted using a broad range of particulate matter (*i.e.* Gelfoam), steel coils, detachable balloons and ethanol for diverse situations (McLean and Meranze, 1986).

### *Renal artery obstruction*

When the aetiology of deteriorating renal function appears to indicate renal artery obstruction, angiography is the procedure of choice. Occlusions are usually secondary to emboli but thrombi may arise spontaneously following surgical manipulation, angiography or angioplasty. Low dose selective infusion of fibrinolytic agents via selective percutaneous renal artery catheterisation is an acceptable alternative to surgery (Cronan and Dorfman, 1983).

### *Retained foreign bodies*

Despite the innumerable constraints placed on the manufacturers of stent catheters, no piece of equipment is 100% fail-safe and fractures can occur in catheters, balloons and ureteric stents during manipulation. At one time, surgical exploration was the only way to retrieve the missing pieces. Now, fluoroscopically guided catheter forceps, graspers, helical baskets and snare wires can achieve this same result (Fritzsche, 1986; Gordon *et al.*, 1986; Saltzman, 1988).

## Conclusion

Not all types of urological complications have been addressed in this review in order to keep the discussion focused on those problems amenable to a radiological diagnosis. Wound infection and dehiscence, intestinal perforation or obstruction, pancreatitis, respiratory distress and issues related to the particular procedure performed are examples of the complications that may arise. Even though diagnostic imaging can play an important role in the investigation of fevers and deteriorating renal function, further discussion of these complications is beyond the scope of this report. Similarly, a description of the urological complications arising following renal transplant surgery requires a prolonged discussion.

When a problem affecting renal function occurs following surgical or endourological manipulation of the urinary tract, the diagnosis is imperative, for there is only a limited window of opportunity for making an accurate diagnosis to ensure preservation of the renal unit. Fortunately, most complications can be readily diagnosed through one or more radiological studies.

As described, nuclear medicine renography provides an assessment of gross excretory function of the kidneys. Intravenous urography also parallels renal function and, like antegrade pyelography, will delineate the anatomy of the collecting system. Cross-sectional imaging by US or CT will provide a precise depiction of the urinary tract and its relation to other intra-abdominal, retroperitoneal or pelvic structures. Ultrasonography plays an important role in defining post-operative fluid collection, hydronephrosis and changes in intrarenal arterial flow. CT, like US, can delineate any abnormalities of fluid collections, and both have the advantage of facilitating percutaneous biopsies, aspirations and drainages.

With the evolution of the angiographic catheter from a diagnostic device into a therapeutic instrument, the approach to the management of urological complications has changed dramatically. Indeed, the diagnostic catheter, or modification thereof, can now be used to decompress the obstructed collecting system, bypass urinary obstruction, drain collections of blood, urine or pus, and increase or decrease arterial flow by dilatation or embolisation.

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# Sequential Renography in Acute Urinary Tract Obstruction due to Stone Disease

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Summary—A group of 76 patients with urographically proven acute calculus obstruction was studied prospectively using $^{99m}$Tc-DTPA renography to see if kidneys at risk of irreversible renal damage could be identified. There was a statistically significant relationship between the presence of obstruction on renography and the subsequent requirement for intervention, but not with the degree of obstruction (partial or severe). Stones over 5 mm in size are highly likely to cause obstruction, a drop in relative renal function and require intervention. In all, 14 patients sustained a drop in relative renal function of $>7\%$ on renography and 12 of these returned to normal limits when their calculi had been passed or removed. The 2 kidneys whose function remained impaired had fallen below 25% of overall renal function and both patients had received prior treatment for their calculi. No patient who presented *de novo* suffered any permanent loss of ipsilateral renal function. The results confirm that the criteria for intervention were well founded and emphasise the importance of achieving a stone-free state after primary treatment. Renography is recommended for stones over 5 mm in size, those in the middle and upper ureter and for those patients discharged with a stone *in situ*.

This study was performed to determine whether there is an incidence of irreversible renal injury associated with acute upper tract obstruction due to stone disease and its management using traditional clinical criteria.

The conventional management of patients with ureteric colic secondary to a ureteric stone is confirmation of the diagnosis by means of intravenous urography, followed by admission for observation and pain relief. Subsequent treatment is then justifiably conservative in the first instance because over 50% of stones are small ($<5$ mm) and are passed spontaneously within 48 h of presentation (Sandegard, 1956).

If this does not occur, the indications for intervention are ill defined but usually include 1 or more of the following: continuing pain, failure of stone progression, stone size, associated infection and a deterioration in renal function (Fox *et al.*, 1965). Apart from infection, the only absolute indication for intervention is a deterioration in renal function, which in the past was an assessment made by intravenous urography.

Only radionuclide evaluation can detect unilateral renal functional change. Using the dynamic agent $^{99m}$Tc-DTPA it is possible to assess the degree of obstruction and quantitate unilateral deterioration in function sequentially.

This prospective study involved patients who presented with a radiologically proven acute upper urinary tract obstruction having sequential radionuclide evaluation. We attempted to determine whether conventional methods of stone management would avoid a deterioration in relative renal function and, if not, whether this functional deficit was reversible following relief.

## Patients and Methods

The study group comprised 76 patients (60 male, 16 female; age range 20–75 years) who were admitted with acute calculus obstruction demonstrated on intravenous urography. All had $^{99m}$Tc-DTPA renograms within 24 h of admission and, if

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obstructed, further renograms at intervals of 72 to 96 h or until the stones had either passed spontaneously or obstruction was relieved. Follow-up renography was performed 3 months after discharge from hospital.

Patients were well hydrated prior to renography, so that urine specific gravity was $\leqslant 1010$, which corresponded to a urinary osmolality of $<600$ mosm/l. This degree of hydration ensured a urine flow rate of $>10$ ml/min in every case. In addition, frusemide (20 mg) was administered after 10 min. Obstruction was classed as severe if the isotope continued to accumulate despite the administration of frusemide and partial if clearance occurred following the diuretic but was incomplete, leaving a significant post-micturition residue in the renal pelvis. Giving frusemide to these patients did not precipitate or aggravate loin discomfort or lead to extravasation or isotope.

$^{99m}$Tc-DTPA renography was performed on an Apex 409 gamma camera with a high resolution collimator. Acquisition continued for 20 min in frame size $128 \times 128$ at a 20-s frame rate. Split function was assessed on the sum of the background subtracted counts over both kidneys between 1 to 2 min of the renogram.

Patients were managed conservatively in the first instance if the stone was under 10 mm in size. Surgical intervention was deemed necessary if a reasonable trial of conservative management was unsuccessful, or in conditions of persistent pain and/or upper urinary tract obstruction. No patient was left obstructed for more than 7 days. The association of obstruction and a temperature or documented urinary infection was considered an absolute indication for intervention.

A drop in relative renal function of more than 7% was considered to be significant and not due to mathematical error. The upper third of the ureter was taken to extend from the renal pelvis to the superior aspect of the bony pelvis, the middle third the portion of ureter in front of the bony pelvis, and the lower third from the inferior aspect of the pelvis to the point of entry of the ureter into the bladder.

The data were analysed using the $\chi^2$ and Mann-Whitney U tests.

## Results

Of those patients whom urography identified as obstructed, 39 (51%) were still obstructed when they underwent $^{99m}$Tc-DTPA renography the day after admission. Of these, 27 (69%) had severe obstruction and 12 (31%) partial obstruction. The presence of obstruction on renography the day after admission and the need for subsequent intervention was statistically significant ($P<0.01$) (Fig. 1), but the degree of obstruction (severe or partial) did not influence the overall outcome (spontaneous passage or surgical intervention) ($P<0.84$). This was explained by the fact that the stones which accounted for the majority of cases of severe obstruction (63% of total) were small ($<5$ mm in size), were most commonly found in the lower third of the ureter and were most likely to pass spontaneously. However, a large stone size is a significant factor in presenting with obstruction ($P<0.04$) and later with an associated drop in relative renal function on renography ($P<0.02$).

It was found that 63% of stones were passed spontaneously, 84% of which were in the lower third of the ureter on presentation, 4% in the middle third and 13% in the upper third (Fig. 2). If one excludes stones larger than 10 mm (which always required operative removal), the size of stone was seen to have a highly significant influence ($P<0.002$) on the eventual outcome. Despite this, 20% of stones under 5 mm in size required operative intervention even after a reasonable trial of conservative management (Figs 3 and 4).

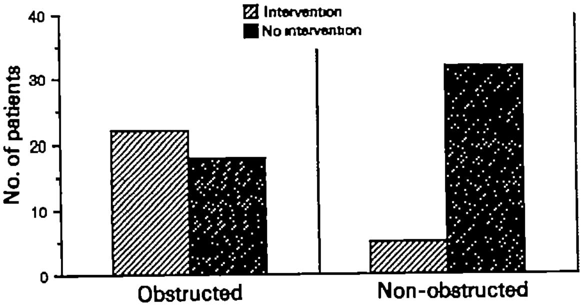

**Fig. 1** Results in relation to renographic findings.

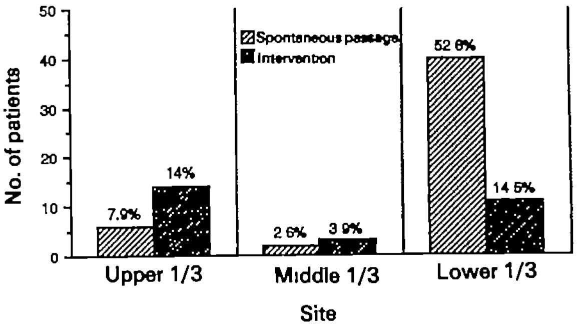

**Fig. 2** Site of stones in relation to outcome.

Relative renal function as demonstrated on the $^{99m}$Tc-DTPA renogram fell in 14 patients (18%) and 79% of these were obstructed on presentation. The association between obstruction and a drop in relative renal function was significant ($P<0.02$). Three patients were unobstructed when they underwent renography, yet showed a drop in function. Of these, 1 had a large stone that had been present for several months and required intervention; the other 2 passed their stones spontaneously within 48 h of admission to hospital.

Of the 14 kidneys with diminished function, 12 (86%) returned to normal levels of split function after removal of the calculi (Table). The overall incidence of permanent functional deficit in this series was therefore 2.6%. Of the 2 patients whose kidneys did not recover following stone treatment, 1 had had a large renal pelvic stone removed surgically 8 years earlier; the other had a 1.5-cm pelviureteric stone which showed no evidence of associated infection but had required lithotripsy at another hospital 2 years previously. Both of these renal units had function of <25% on the affected side on presentation (16 and 22% respectively), which may have represented their residual functional capacity following previous uropathic damage.

**Table** Treatment of Patients who Sustained a Drop in Function

| *Type of treatment* | *No of patients* |
|---|---|
| "Push bang" | 5 |
| Spontaneous passage | 3 |
| Percutaneous removal | 3 |
| Percutaneous nephrostomy | 2 |
| Ureteroscopic extraction | 1 |

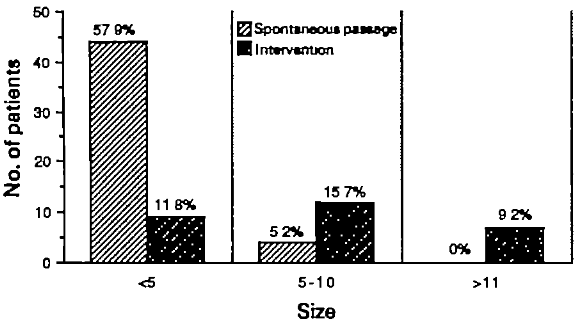

**Fig. 3** Size of stones in relation to outcome.

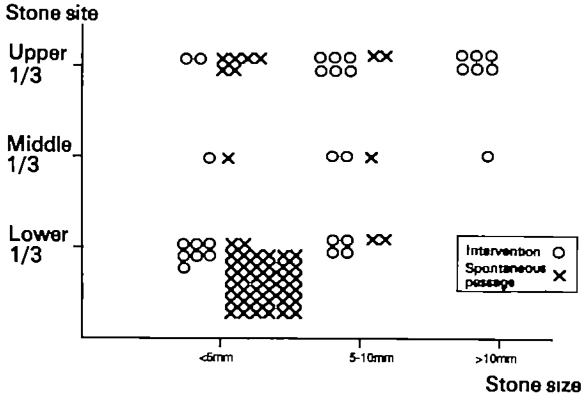

**Fig. 4** Influence of stone site and size on outcome.

At the outset it was planned that the performance of renography would not influence the management of patients. However, renography did identify a small group who had become pain-free despite persistence of obstruction. This group was then managed as were the other obstructed patients.

## Discussion

The various methods of dealing with calculi in the renal pelvis and ureter have received considerable attention in the past decade, but the functional change in the kidney above the site of obstruction has been largely neglected.

Two comprehensive series quote the incidence of severe renal functional impairment following an episode of stone obstruction to be less than 1% (Sandegard, 1958; Fox *et al.*, 1965). All of these patients had urinary infection and all had interventional rather than conservative management. Intravenous urography was used as a measure of renal function. Although urography is a good index of gross function, it is a poor indicator of the relative functional difference between 2 kidneys and cannot accurately determine the degree of obstruction.

Of 76 patients admitted with acute upper tract obstruction due to calculus disease, 39 (51%) were obstructed on renography the following day; 22 (56%) ultimately required operative intervention on conventional criteria. All of the patients who were obstructed on admission yet did not require intervention because they had passed their stones spontaneously had stones under 5 mm in size (Fig. 1). All of those patients who were unobstructed yet required an operation because of lack of stone progression had stones greater than 5 mm in size. In this series the combination of obstruction and stone size exceeding 5 mm invariably required intervention. Although a high proportion of obstructive patients had stones under 5 mm, these stones are likely to pass spontaneously and can certainly be treated conservatively in the first instance, since no permanent functional deficit was caused by this type of stone.

No calculus presenting *de novo* in this series led to a permanent renal injury as demonstrated on $^{99m}$Tc-DTPA renography. The 2 stones that were associated with a permanent drop in function were both lodged at the pelviureteric junction and the patients had had previous treatment. This demonstrates the importance of achieving a stone-free state prior to discharge from care. This is highlighted by the fact that the only other patient who had a unilateral drop in function to below 25% and yet returned to normal (46%), was a man with a 2-cm renal pelvic stone inadequately treated by lithotripsy who subsequently required percutaneous nephrolithotomy to ensure complete clearance of residual fragments.

One of the major difficulties in treating patients with ureteric stones who present with acute obstruction that settles is when, if at all, intervention should occur if the stone remains *in situ*. To a certain extent this depends on the treatment modalities available to the surgeon but we suggest the following guidelines.

1. Small (<5 mm) stones anywhere in the ureter will pass spontaneously in over 90% of cases, mostly within 48 h. Intervention should be reserved for those that cause persistent symptoms or obstruction.
2. Medium-sized stones (5–10 mm) can be treated conservatively in the first instance. The probability of their requiring intervention is high, especially when lodged in the middle or upper ureter and when associated with obstruction.
3. Large stones (>10 mm) should be treated promptly regardless of their site, since these stones are unlikely to pass spontaneously (Sandegard, 1956) and are associated with a higher incidence of complications if left *in situ*.

We found sequential renography to be useful in this group of patients for the following reasons.

1. Patients were discharged if renography was normal: of 37 patients treated in this way, only 2 were readmitted with further pain.
2. It identified a group of patients who had become pain-free yet were still obstructed. This situation arose in cases where pain had persisted for more than 3 to 4 days and then eased despite the demonstration of severe obstruction on renography. These patients would not have been treated if the renograms had not been performed and they may be similar to the patients reported by Older *et al.* (1976) and Craven and Lecky (1970), where follow-up urography revealed silent post-obstructive renal atrophy.
3. It differentiated clearly between partial and complete obstruction, allowing close supervision of those patients at greater risk.
4. The quantitative assessment of relative renal function each time a patient was scanned facilitated management decisions.
5. If used sequentially to monitor progress, the received radiation dose is lower than that following urography (IVU radiation dose 4.36mSv per study, DTPA scan 2mSv per study (Shrimpton *et al.*, 1986).

Since the only patients in this study to suffer a permanent fall in relative renal function were those who had had inadequate stone clearance on their first admission, a stone-free state following treatment must be the aim in all cases.

The identification of the small group of patients who had persistent obstruction yet were pain-free highlights the importance of not discharging patients from hospital without ensuring that they are unobstructed or that their stone has been successfully treated.

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# Is there a Place for Conservative Surgery in the Treatment of Renal Carcinoma?

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Summary—Since 1981, 31 patients have undergone conservative surgery for malignant renal tumours and have been followed up for at least 2 years. The techniques included enucleation or resection (wedge resection or partial nephrectomy).

In 10 patients the indications for kidney-sparing surgery were absolute, while in the remainder the conservative surgical approach was a deliberate choice. The tumours varied in diameter from 1.3 to 12 cm and no metastases were detected on pre-operative screening.

One patient died post-operatively from myocardial infarction. In the remaining 30 there were no local recurrences. Two patients died from skeletal metastases (1 with bilateral malignancy) and 2 underwent surgery in the post-operative period for haemorrhagic complications.

The efficacy of conservative surgery in the local control of renal cancer is an argument in favour of its wider use.

In recent years the incidence of small renal tumours has increased, perhaps because of an increasing number of carcinogens in the environment, but also because of the improved specificity of modern diagnostic techniques (Curry *et al.*, 1986). Most of these tumours are detected before symptoms occur and their malignant potential in relation to their size was discussed by Curry *et al.* (1986). Today the choice of treatment, radical as opposed to conservative surgery, is a matter of major concern. Radical nephrectomy, with or without lymph node dissection, has been the treatment of choice, although unexpectedly good results have been achieved with local tumour resection (Graham and Glenn, 1979; Marberger *et al.*, 1981; Smith *et al.*, 1984; Bazeed *et al.*, 1986; Novick *et al.*, 1989; Novick, 1987; Carini *et al.*, 1988; Montie and Novick, 1988; Schärfe *et al.*, 1988; Jung *et al.*, unpublished data).

Elective conservative surgery in the presence of a normal contralateral kidney has been severely criticised (Mukamel *et al.*, 1988; Skinner, 1989), although the results of such treatment have been excellent (Carini *et al.*, 1988; Schärfe *et al.*, 1988). We reviewed our data to see if a less aggressive approach might be appropriate for some renal tumours.

## Patients and Methods

Since 1981, 31 patients with renal adenocarcinoma have undergone conservative surgery. Their selection was based on definitive pathological examination and they formed part of a large group of patients who underwent local excision for different types of renal masses, both benign and malignant. Oncocytomas were not included.

In 10 of these 31 patients (12 females and 19 males), aged between 28 and 88 years (mean 56.9), the indication for conservative surgery was unequivocal, while in 21 patients the decision was taken electively (Table 1). The tumours ranged in size from 1.3 to 12 cm and no detectable regional lymph node involvement or distant metastases were found at the time of surgery. All tumours were investigated pre-operatively by means of ultrasound and dynamic CT scan, using 4 to 5 mm slices, but only in cases where arterial control could be useful during

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**Table 1** Distribution of Patients undergoing Non-elective or Elective Conservative Surgery for Renal Carcinoma

| | *Male* | *Female* | *Total* |
|---|---|---|---|
| Non-elective | 6 | 4 | 10 |
| Solitary kidney | 4 | | 4 |
| Contralateral hypoplasia | 1 | 3 | 4 |
| Bilateral cancer | 1 | 1 | 2 |
| Elective | 13 | 8 | 21 |

surgery was selective renal arteriography undertaken.

The operation was performed through an extended lumbotomy above the twelfth rib, which was usually resected. Hilar clamping was not done as a rule. Either simple tumour enucleation or a resection in healthy tissue (wedge resection or partial nephrectomy) was performed. Tumour enucleation with frozen section of the tumour bed was performed in 2 early cases and in 1 patient with a large cystic necrotic adenocarcinoma. Larger tumours were resected when possible after selective ligation of arterial branches as indicated by the pre-operative arteriogram. Wedge resection and partial nephrectomy provided a far greater safety margin. The resected specimen was immediately sent for frozen section of the resection margins.

**Table 2** Patients, Methods and Results of Kidney-sparing Surgery

| *No.* | *Initial* | *Age (years)* | *Sex* | *Necessary elective* | *Size (cm)* | *Technique* | *Stage, grade* | *Follow-up (months)* | *Complications* | *Result* |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | L.L | 68 | M | Solitary kidney | 7.5 | Part. | $T_3G_{III}$ | 3 days | C.V. death | — |
| 2 | D.R.A. | 66 | M | Bilat. tumours | 4.0 | Part. | $T_1G_{II}$ | 18 | — | Death (metastasis) |
| 3 | T.A. | 67 | M | Elective | 4.0 | Part. | $T_2G_I$ | 21 | — | Death (metastasis) |
| 4 | C.P. | 34 | M | Elective | 1.5 | Part. | $T_1G_{II}$ | 24 | — | Tumour-free |
| 5 | J.J. | 62 | M | Solitary kidney | 4.4 | Part | $T_2G_{II}$ | 24 | — | Tumour-free |
| 6 | V F.F. | 44 | M | Elective | 2.5 | Part. | $T_2G_I$ | 24 | — | Tumour-free |
| 7 | B.H. | 65 | F | Contralateral hypoplasia | 3.5 | Part | $T_2G_I$ | 25 | — | Tumour-free |
| 8 | B G. | 55 | F | Elective | 6.0 | Part. | $T_2G_I$ | 27 | — | Tumour-free |
| 9 | V.D.E. | 63 | F | Elective | 6.0 | Part. | $T_2G_{II}$ | 27 | Splenic haemorrhage | Tumour-free |
| 10 | L.M. | 46 | F | Elective | 4.0 | Part. | $T_3G_{II}$ | 27 | Heparin haemorrhage | Tumour-free |
| 11 | S.H. | 60 | M | Elective | 2.6 | Part. | $T_2G_{III}$ | 30 | — | Tumour-free |
| 12 | V.S.M. | 55 | F | Contralateral hypoplasia | 7.0 | Part. | $T_3G_I$ | 32 | — | Tumour-free |
| 13 | I.A. | 61 | M | Solitary kidney | 6.0 | Part. | $T_3G_{III}$ | 32 | — | Tumour-free,<br>C.V. death |
| 14 | C.E. | 57 | F | Elective | 3.0 | Part. | $T_2G_{II}$ | 33 | — | Tumour-free |
| 15 | S.A | 57 | M | Elective | 2.7 | Part. | $T_2G_I$ | 34 | — | Tumour-free |
| 16 | V.A. | 28 | F | Elective (v.H.L.) | 2.0 | Part. | $T_2G_I$ | 36 | — | Tumour-free |
| 17 | G.J | 88 | F | Elective | 2.5 | Part | $T_1G_{II}$ | 36 | — | Tumour-free |
| 18 | B.L. | 66 | M | Contralateral hypoplasia | 7.0 | Part. | $T_3G_I$ | 36 | — | Tumour-free,<br>C.V. death |
| 19 | R.A. | 76 | M | Elective | 2.0 | Part. | $T_1G_I$ | 37 | — | Tumour-free |
| 20 | L.P. | 51 | F | Bilat. tumours | 1.7 | Part. | $T_1G_I$ | 42 | — | Tumour-free |
| 21 | D.M.G | 54 | M | Elective | 12 | Enucl. | $T_3G_{III}$ | 43 | — | Tumour-free |
| 22 | D.W.M. | 58 | F | Elective | 1.3 | Part. | $T_1G_I$ | 44 | — | Tumour-free |
| 23 | T.E. | 51 | F | Contralateral hypoplasia | 5.0 | Part. | $T_2G_{III}$ | 48 | — | Tumour-free |
| 24 | U.L. | 72 | M | Elective | 2.0 | Part. | $T_1G_I$ | 56 | — | Tumour-free |
| 25 | J.M. | 45 | M | Elective | 2.5 | Part. | $T_1G_{II}$ | 57 | — | Tumour-free |
| 26 | P.A | 53 | F | Elective | 1.5 | Part. | $T_1G_I$ | 58 | — | Tumour-free,<br>nephrectomy |
| 27 | W.G. | 58 | M | Elective | 2.0 | Part | $T_1G_I$ | 60 | — | Tumour-free |
| 28 | V.S.M | 56 | M | Elective | 2.5 | Part | $T_1G_{II}$ | 64 | — | Tumour-free |
| 29 | V.D.Z. | 44 | M | Elective | 1.8 | Part. | $T_1G_I$ | 64 | — | Tumour-free |
| 30 | G.R. | 53 | M | Elective | 3.5 | Enucl. | $T_1G_I$ | 64 | — | Tumour-free |
| 31 | G.P. | 51 | M | Solitary kidney | 3 | Enucl. | $T_2G_{II}$ | 106 | — | C.V. death |

V.H.L. = von Hippel-Lindau; C.V. = Cardiovascular, Part. = partial resection; Enucl. = enucleation

Following the 1983 TNM classification (Schröder *et al.*, 1988), 13 tumours were T1, 12 were T2 and 6 were T3. Five patients had G3 tumours (Table 2).

Follow-up in all cases consisted of blood analysis, chest X-ray and kidney and liver ultrasound examination every 3 months during the first year, at 6-monthly intervals during the second year, and thereafter on a yearly basis. Computed tomography was performed every year.

## Results

One male patient died from myocardial infarction 3 days post-operatively. A female patient, having had a partial nephrectomy underwent further surgery 4 days post-operatively because of bleeding following heparin treatment of a suspected pulmonary embolism. No significant bleeding site was found and she quickly recovered. Another female patient, having had a wedge resection of the left upper pole, underwent splenectomy for a secondarily ruptured subcapsular haematoma of the spleen. Six weeks later she presented with acute renal obstruction due to blood clots filling the excretory system. Nephrostomy quickly restored renal function and after removal of the nephrostomy tube she made a satisfactory recovery. The other patients had no post-operative problems and recovered well (Table 2).

None of the 30 patients followed up for 18 to 106 months (mean 41) has shown any evidence of local tumour recurrence. Three patients died after cardiovascular insults without tumour activity at 32, 36 and 106 months. A female patient underwent radical nephrectomy after 26 months for suspected tumour recurrence on CT scan. Pathological examination revealed only scar tissue and a thick-walled hydrocalix without malignancy. Two patients developed general metastatic disease and died after 18 and 21 months without local recurrence; 1 of them had synchronous bilateral cancer for which he had a radical nephrectomy on one side for a T3 tumour. A patient with von Hippel-Lindau disease underwent conservative surgery 6 months after the first operation for contralateral tumours which proved to be atypical cysts.

All tumours were single. In 1 case a small subcutaneous tumour on the cytological puncture tract was removed during the same procedure. Another patient who had been investigated elsewhere had a diagnostic puncture that gave rise to focal bleeding, dissecting the tumour from the surrounding capsule.

A patient who was scheduled for wedge resection of a presumably solitary tumour was found to have 3 small satellite lesions (3 mm) and subsequently underwent radical nephrectomy.

## Discussion

There is no doubt about the indications for conservative surgery in certain circumstances (Graham and Glenn, 1979; Marberger *et al.*, 1981; Smith *et al.*, 1984; Novick *et al.*, 1989), in von Hippel-Lindau disease (Grant and Taylor, 1987; Skinner, 1989) and in patients with a familial tendency (Pathak *et al.*, 1982). One of the arguments against elective conservative surgery for renal carcinoma is the possibility of multi-focal disease (Mukamel *et al.*, 1988; Skinner, 1989), while an argument in favour of an elective kidney-sparing approach is the pre-operative uncertainty about malignancy.

Modern imaging techniques can define accurately the histopathological nature of a renal tumour in many cases, but there may still be doubt about eventual malignancy (Curry *et al.*, 1986; London *et al.*, 1989). We have previously carried out ultrasound or CT guided punctures. Puncture can give accurate information but there is a risk of bleeding and tumour spread (Wehle and Grabstald, 1986), the latter complication having occurred in 1 of our patients. The false negative and false positive results of pre-operative puncture are well documented (Helm *et al.*, 1983; Bazeed *et al.*, 1986; Curry *et al.*, 1986; Mukamel *et al.*, 1988). When deciding to remove a small solid tumour by tissue-sparing means, pre-operative pathological differentiation becomes superfluous and puncture can even be dangerous, compromising a safe tumour resection. The only reason for solid renal mass puncture would be measurement of its DNA content, which could indicate whether radical or conservative surgery should be undertaken (Klöppel *et al.*, 1986).

Before considering partial resection of a renal tumour a dynamic CT scan with 4 mm slices was carried out. This proved useful in delineating the tumour and indicating multifocality (London *et al.*, 1989). Magnetic resonance imaging (MRI) is equally accurate and could perhaps provide further information (Strake *et al.*, 1988). Although anatomical studies of autopsy and radical nephrectomy specimens showed a considerable number of satellite lesions (Bennington, 1973; Mukamel *et al.*, 1988), our pre-operative assessment of solitary lesions was inaccurate on only one occasion. Stripping the renal capsule is unnecessary but it is important to inspect the whole capsule for satellite lesions after partial resection. Should they be found, radical nephrectomy is indicated.

Other technical points are a matter of debate. Clamping the hilus with or without hypothermia and bench surgery has been suggested (Wickham, 1975; Marberger *et al.*, 1981; Smith *et al.*, 1984; Novick, 1987) but others have advocated either digital compression of the renal artery (Graham and Glenn, 1979) or *in situ* surgery without vascular control (Bazeed *et al.*, 1986; Schärfe *et al.*, 1988). We have not used hilar clamping as a rule because secondary arterial thrombosis has been reported (Carini *et al.*, 1988). In our series all tumours were resected *in situ* and hilar clamping was done only when haemorrhage could not be controlled immediately. *Ex vivo* surgery was avoided because of its increased complication rate (Wickham, 1975). Postoperative complications in the present series, even in older patients, were comparable to those of other conservative surgical series (Carini *et al.*, 1988; Schärfe *et al.*, 1988), although the morbidity rate following a haemorrhage exceeds that of radical surgery (Grayhack, 1983).

The choice of surgical technique is controversial. Although it seems logical that partial nephrectomy or a wedge resection in healthy tissue is safer than enucleation or excavation, some authors have reported better results with excavation (Carini *et al.*, 1988) or have advocated enucleation for von Hippel-Lindau disease or for hilar tumours (Novick *et al.*, 1989). Although it has been suggested that local recurrence is unrelated to the resection technique (Graham and Glenn, 1979), we believe that a margin of normal parenchyma should always be removed. This approach is supported by pathological reports showing invasion of the pseudocapsule (Smith *et al.*, 1984; Novick, 1987). The resected margins are examined on frozen section and we have never encountered a positive frozen section. Should this occur, a more extensive resection would be essential. In an elective setting it would mean radical nephrectomy. The role of tumour bed coagulation (Bazeed *et al.*, 1986) is not established.

The results of this study confirm the feasibility of local control of renal cancer by conservative surgery, as previously demonstrated in circumstances where there was no alternative (Graham and Glenn, 1979; Marberger *et al.*, 1981; Smith *et al.*, 1984; Novick *et al.*, 1989) and also in elective cases (Carini *et al.*, 1988; Schärfe *et al.*, 1988; Jung *et al.*, 1989 (unpublished data). The characteristics of clear cell carcinoma explain why successful results can be achieved, since the tumour, arising in the renal cortex, is surrounded by a pseudocapsule and rarely invades the renal capsule (Graham and Glenn, 1979; Marberger *et al.*, 1981; Bazeed *et al.*, 1986; Novick *et al.*, 1989).

Medico-legal implications may have discouraged the extension of the indications for kidney-sparing surgery in patients with localised and well defined solitary tumours and a normal contralateral kidney.

Preservation of renal function, erroneous nephrectomy for a benign lesion, damage to the contralateral kidney and the possibility of contralateral recurrence are poor arguments in favour of conservative surgery, according to Montie and Novick (1988); personal experience and anecdotal reports are poor arguments against elective conservative surgery (Skinner, 1989). Only a large randomised trial could answer this question (Montie and Novick, 1988), but it is undeniably true that local control following elective surgery cannot be improved upon, since no local recurrences have been reported (Table 3). Two patients had metastatic disease and it is doubtful whether radical nephrectomy would have influenced this outcome. Our results were undoubtedly influenced by positive selection of patients. The most important point is to define the indications for conservative resection. We feel that solid parenchymal tumours should not always be subjected to radical nephrectomy and that conservative surgery should not be restricted to von Hippel-Lindau disease or to patients where preservation of renal function is a relevant clinical consideration (Novick *et al.*, 1989).

Our follow-up period is probably too short for definite conclusions to be drawn on local recurrence rates, since recurrences can occur 20 years after treatment of the primary tumour (Topley *et al.*, 1984). However, as in other fields of oncological surgery, the trend towards kidney-sparing surgery will continue because an increasing number of small solid tumours are detected incidentally on ultrasonography or CT scan. It seems reasonable

**Table 3** Number of Local Recurrences after Kidney-sparing Surgery

| | *No.* | *Elective* | *Necessary* |
|---|---|---|---|
| Smith *et al.* (1984) | 43 | — | 3/43 |
| Schärfe *et al* (1988) | 84 | 0/52 | 2/32 |
| Carini, *et al* (1988) | 36 | 0/20 | 1/16 |
| Novick *et al* (1989) | 100 | — | 9/100 |
| Jung *et al.* (unpublished data) | 36 | 0/36 | — |
| This series (1990) | 30 | 0/20 | 0/10 |
| Total | 330 | 0/128 | 15/202 (7.5%) |

not to perform radical nephrectomy for these small, low grade carcinomas when there is no risk of leaving neoplastic tissue behind.

The absolute criteria for elective conservative surgery (without considering von Hippel-Lindau disease or familial predisposition) can be summarised as follows. The tumour should be solitary and well demarcated; there should be no involvement of perinephric fat and the tumour should be localised, *i.e.* easily resectable by wedge resection or partial nephrectomy rather than by enucleation. Per-operatively, the margins of the resection should be examined on frozen section. If the results are either doubtful or positive, a nephrectomy should be done. Post-operatively the patient should be followed up very closely. He should be aware of the possibility of recurrence and agree to a strict post-operative follow-up regime with ultrasound and CT scan. An unco-operative patient should not undergo elective conservative surgery and any suspicion of recurrence on follow-up should be followed by radical nephrectomy.

While we are prepared to compare radical and partial resection in a randomised study, we believe that at the present time our kidney-sparing approach is justified in situations where the relevant criteria and conditions are fulfilled.

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# Effect of Abdominal Straining on Urinary Flow Rate in Normal Males

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Summary—The measurement of urinary flow rate by uroflowmetry and its relationship to voided volume and age have been extensively studied. It is well recognised that some men void with abdominal straining, but any effect of this on the urinary flow rate is usually not taken into account in urological practice.

The aim of this study was to determine whether abdominal straining had any significant influence on the urinary flow rate. Three male volunteers performed multiple voidings either with or without abdominal straining. Statistical transformation of the data and the use of co-variant analysis allowed a comparison between "normal" or passive voiding and voiding with abdominal straining. The results showed that abdominal straining caused a significant improvement in both the average and maximum urinary flow rate. If the effect of abdominal straining is not taken into account during the interpretation of uroflowmetry results, incorrect conclusions may be made which could influence subsequent management. It is suggested that the method of voiding should be standardised by instructing patients, if possible, to avoid abdominal straining during uroflowmetry assessment.

The use of uroflowmetry in the diagnosis of outflow obstruction has become widespread in clinical practice as well as in clinical and laboratory research. There is continuing reluctance by some urologists to accept the results that uroflowmetry provide because of the known effects that voided volume and age have on the flow parameters (Drach *et al.*, 1979). Various attempts have been made to adjust for these effects, probably the best known being the nomograms produced by Siroky *et al.* (1979). There remains a large variation between individuals which makes categorisation of a single individual difficult. In addition, there is variability with each individual flow rate, suggesting that there may be other important contributing factors.

Variation in the urinary flow rate due to changes in abdominal pressure has been recognised in pressure-flow studies where intra-abdominal pressure is measured with a rectal probe (Abrams and Feneley, 1978). Observations of male patients voiding show that while some void with no apparent effort, others attempt to maximise their flow with considerable abdominal straining. When questioning patients about their voiding method, some use abdominal straining as the usual method of voiding to overcome the outflow obstruction. Others do not ordinarily strain but do so in the belief that the flow test is being performed to show maximal results rather than the usual results. Similar answers are received from patients undergoing flowmetry who have neurogenic bladders, urethral strictures or indeed volunteers who take part in flowmetry studies.

Having recognised that some patients do void during flowmetry using abdominal straining, the authors elected to examine whether any change in flow rate resulting from this is significant and may therefore cause spurious interpretation of the flowmetry results.

## Materials and Methods

Three adult male volunteers aged between 30 and 40 years performed multiple flow tests over a period

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of 3 months. No volunteer had lower urinary tract symptoms or a history of previous surgery or injury to the urinary tract. A Dantec Urodyn 1000 mictiograph was calibrated using a constant flow rate (Hinman and Cox, 1967). This was checked against the machine's automatic self-calibration function. Voiding studies were conducted in private in the standing position and were randomly performed either passively or with abdominal straining to produce as great a flow rate as possible (this is referred to as active voiding). Since the individuals were normal, it was assumed that the bladders emptied completely and that the voided volume was synonymous with bladder volume at the start of micturition. Thus the voiding abilities of the subjects were not overestimated, as can occur in the presence of residual urine (Siroky *et al.*, 1979).

Factors measured were the maximum flow rate, voiding time and voided volume (by calibrated flask). The average flow rate was calculated as voided volume divided by voiding time. There was no lower limit on voided volumes, as flow rates from all volumes were regarded as valid (Ryall and Marshall, 1982).

Parametric statistical techniques were used by transformation of the data using log and inverse functions. Parabolic ($\ln Q = \ln b + m.\ln V$), hyperbolic ($1/Q = m.1/V + b$) and logarithmic ($Q = b + m.\ln V$) functions were examined, where Q is the flow rate (ml/sec) and V is the voided volume (ml). The slope and intercept of the straight regression line are represented by m and b respectively. Co-variant analysis was used to compare the straight regression lines. Nomograms were constructed using the polynomial regression line and the standard errors this generated.

## Results

The data from each subject were analysed independently. Separate voiding curves were constructed for active and passive voiding. The polynomial regression line demonstrates the characteristic initial steep slope of the voiding curve followed by the plateau phase (Fig. 1). The curves

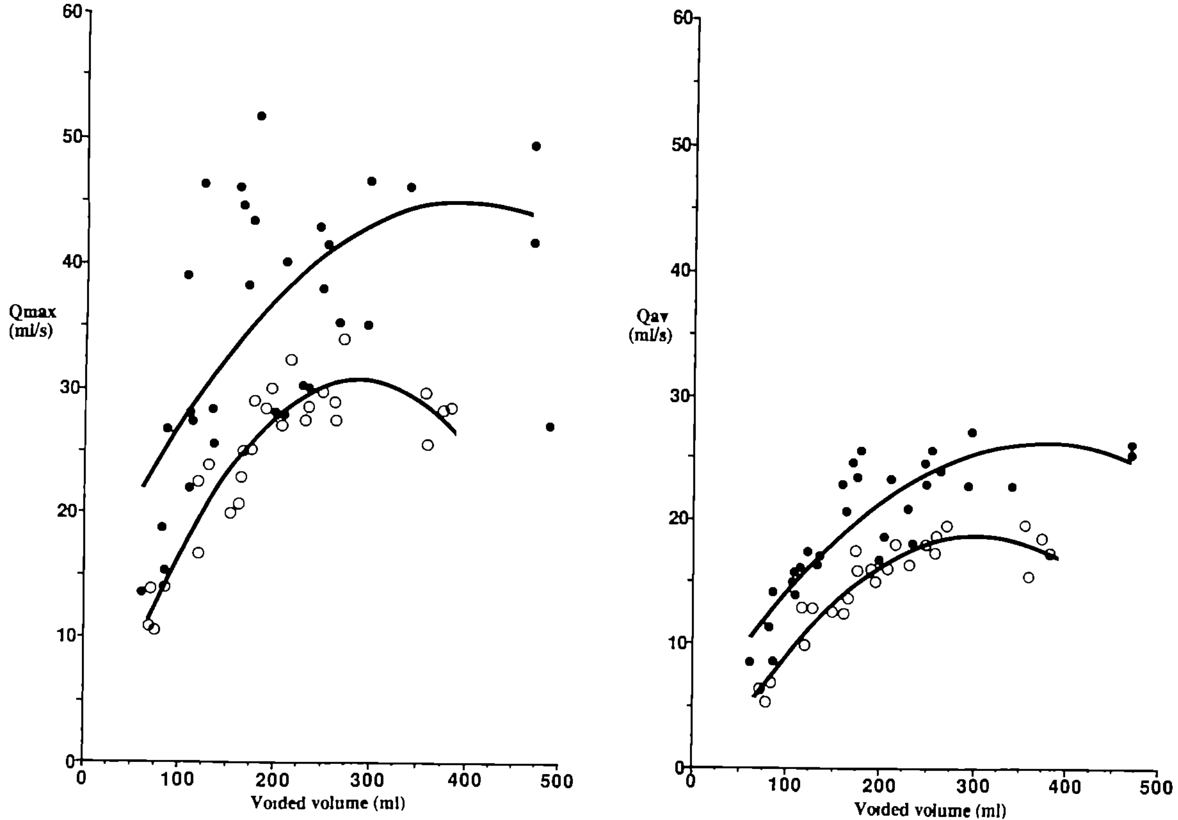


Fig. 1 Voiding curves for a single subject showing the effect of active (●) and passive (○) voiding on the maximum ($Q_{max}$) and average ($Q_{av}$) flow rates

**Table 1** Correlation Coefficients (r) of the Voiding Curves for Active and Passive Voiding for all 3 Subjects using Transformed Data

| | *Subject* | | | | | |
|---|---|---|---|---|---|---|
| | *1* | | *2* | | *3* | |
| | | | Maximum flow rate | | | |
| | Active | Passive | Active | Passive | Active | Passive |
| Parabolic | 0.70 | 0.86 | 0.92 | 0.64 | 0.66 | 0.72 |
| Hyperbolic | 0.80 | 0.92 | 0.93 | 0.86 | 0.59 | 0.94 |
| Logarithmic | 0.66 | 0.86 | 0.93 | 0.60 | 0.63 | 0.65 |
| | | | Average flow rate | | | |
| | Active | Passive | Active | Passive | Active | Passive |
| Parabolic | 0 85 | 0.91 | 0.94 | 0.75 | 0.67 | 0.72 |
| Hyperbolic | 0.89 | 0 95 | 0.93 | 0.90 | 0.64 | 0.94 |
| Logarithmic | 0.86 | 0.92 | 0.94 | 0.72 | 0.61 | 0.63 |

All values of r are significant ($P < 0.01$).

**Table 2** Significance Levels ($P$) showing the Difference between Active and Passive Voiding on the Slope and Intercept for all 3 Subjects using Transformed Data

| | *Subject* | | | | | |
|---|---|---|---|---|---|---|
| | *1* | | *2* | | *3* | |
| | | | Maximum flow rate | | | |
| | Slope | Intercept | Slope | Intercept | Slope | Intercept |
| Parabolic | 0.48 | <0.001 | 0.001 | | 0.33 | <0.001 |
| Hyperbolic | 0.01 | | 0.008 | | 0.001 | |
| Logarithmic | 0.47 | <0.001 | 0.001 | | 0 82 | <0.001 |
| | | | Average flow rate | | | |
| | Slope | Intercept | Slope | Intercept | Slope | Intercept |
| Parabolic | 0.04 | 0.001 | 0.001 | | 0.34 | <0.001 |
| Hyperbolic | 0.001 | | 0.001 | | 0.001 | |
| Logarithmic | 0.51 | 0.001 | 0.001 | | 0.53 | <0.001 |

for both active and passive voiding have similar characteristics. The data for both maximum and average flow rates were examined following transformation, with the results showing that the parabolic, hyperbolic and logarithmic models were all valid ($P < 0.01$) (Table 1). An example of a plot following parabolic transformation is shown in Figure 2.

The transformed data for active and passive voiding were compared using a co-variant analysis (Table 2). This showed a significant difference in either slope or intercept in each model and therefore

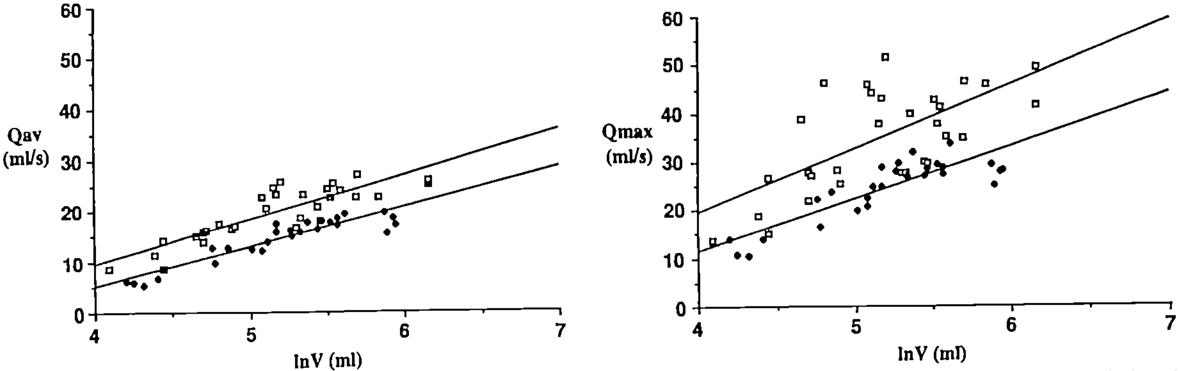


**Fig. 2** Voiding curve following transformation using a parabolic model ($\ln Q = \ln b + m.\ln V$) showing the effect of active (□) and passive (●) voiding on the maximum ($Q_{max}$) and average ($Q_{av}$) flow rates.

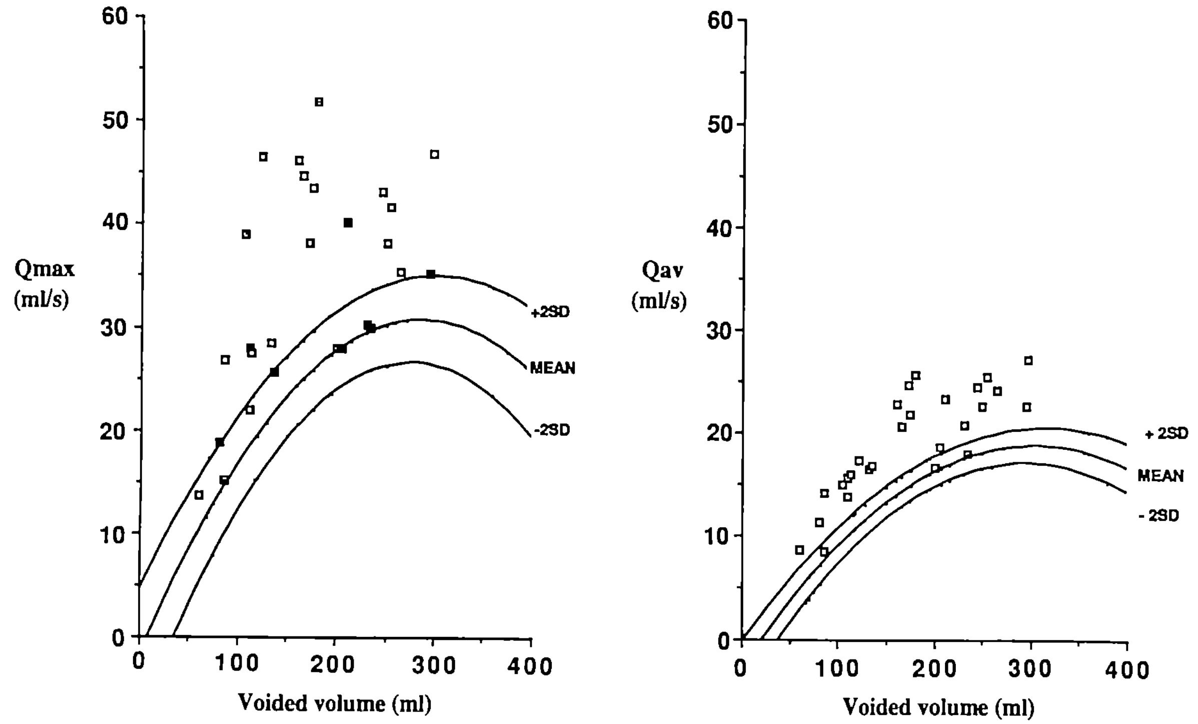
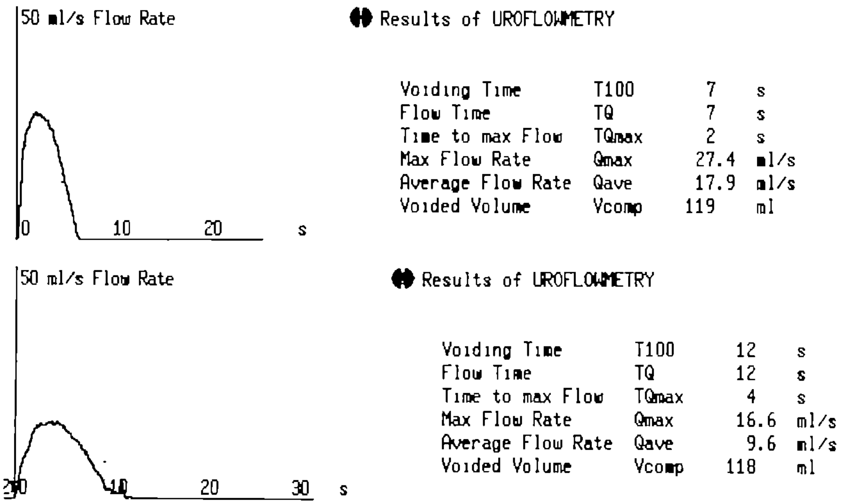


Fig. 3 Voiding curves showing the difference between active and passive voiding for maximum ($Q_{max}$) and average ($Q_{av}$) flow rates. The solid curves (mean, +2 standard deviations, −2 standard deviations) are derived from data from a series of passive flows. The open squares are data from a series of active voids (abdominal straining) from the same individual.



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Results of UROFLOWMETRY

Voiding Time         T100      7    s
Flow Time            TQ        7    s
Time to max Flow     TQmax     2    s
Max Flow Rate        Qmax     27.4  ml/s
Average Flow Rate    Qave     17.9  ml/s
Voided Volume        Vcomp   119    ml
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Results of UROFLOWMETRY

Voiding Time         T100     12    s
Flow Time            TQ       12    s
Time to max Flow     TQmax     4    s
Max Flow Rate        Qmax     16.6  ml/s
Average Flow Rate    Qave      9.6  ml/s
Voided Volume        Vcomp   118    ml
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Fig. 4 Uroflowmetry traces from a single subject with (upper trace) and without (lower trace) abdominal straining.

indicated that abdominal straining significantly improved both the average and maximum (peak) urinary flow rates.

To show more clearly the effect of abdominal straining a nomogram using the passive data from 1 volunteer was constructed with curves of +2 and −2 standard deviations (Fig. 3). When the data for active voiding from the same volunteer are overlaid it can be seen that most of the data points lie outside the +2 standard deviation line.

Two complete flowmetry traces (Fig. 4) from 1 volunteer were selected for active and passive voiding with similar voided volumes (active flow trace = 119 ± 2 ml; passive flow trace = 118 ± 2 ml). Both of these traces show a smooth and uninterrupted curve, demonstrating that a trace produced with abdominal straining is not necessarily recognised by its form.

## Discussion

The peak urinary flow rate is now generally accepted as the most useful parameter for determining an individual's voiding ability. Earlier concern at the usefulness of the flow test was caused by difficulty with the interpretation of the results—particularly for low voided volumes, where some of the earlier flowmeters were inaccurate in the measurement of peak flow, and the belief that high individual variation in flow rate at low voided volumes would make reliable interpretation impossible (Drach *et al.*, 1979). However, more recent studies have shown that data obtained for low and high volumes are valid and that the dependence of peak flow rate on voided volume can be adequately described by parabolic, logarithmic and hyperbolic functions (Ryall and Marshall, 1982; Marshall *et al.*, 1983).

Population studies have demonstrated a wide variability in voiding potential between individuals. This is illustrated by the original flow rate nomograms of Siroky *et al.* (1979), where confidence bands of 1, 2 and 3 standard deviations from the mean are shown. Some of this variability is due to differences in age, with increasing age having an adverse effect on maximum and average flow rates (Drach *et al.*, 1979, 1982). However, even in the recent Liverpool nomograms, which have been stratified for age, there remains considerable spread about the mean curve (Haylen *et al.*, 1989). A similar, although less marked variability, is seen when multiple voidings from a single individual are examined. Siroky *et al.* (1979) empirically estimated this individual variability to be 60% of the population variability and hence a change in flow rate of more than 1.2 standard deviations unlikely to be due to chance alone.

The construction of nomograms describing the relationship between peak flow rate and voided volume has allowed some indication of the "normal" flow rate for a given voided volume. The nomograms also allow us to determine whether a "low" flow rate from an individual is indeed significantly reduced. Despite the apparent usefulness of flow rate nomograms, however, clinicians are still confronted with patients who describe poor voiding ability and yet their peak flow rate would suggest that their voiding is normal. In these cases the decision to proceed with an operation or treatment may be deferred on the grounds that the flow rate is a more reliable indicator of voiding dysfunction than the patient's symptoms. In the course of studying flow rate characteristics it became apparent to us that different patients void with different effort. Some men void without any apparent use of abdominal pressure and some void consistently with considerable abdominal straining. The results of this study have shown that both the average and peak flow rates are significantly improved by the use of abdominal straining. This is clearly seen with the flow volume curves (Fig. 1), which also demonstrate their otherwise similar characteristics, *i.e.* even with abdominal straining the initial steep slope, plateau phase and reduction in flow rate at higher volumes are retained. From these, it would appear impossible to distinguish between the 2 methods of voiding. Furthermore, examination of a single uroflowmetry trace may provide no indication that the patient is voiding with abdominal straining (Fig. 4).

In patients with symptoms of outflow obstruction what may be overlooked is that in many instances the actual obstruction is being overcome by abdominal straining with a coincident normalising of the flow rate. This could account for some of the variability seen with the nomograms (Siroky *et al.*, 1979; Drach *et al.*, 1979, 1982; Haylen *et al.*, 1989) and also the inability of discriminant analyses to define a symptom complex which would accurately predict those with abnormal peak flow rates (Herbison *et al.*, 1988). In addition, the correlation between cystometrographic evidence of lower urinary tract obstruction and flowmetry results has not been ideal (Turner Warwick *et al.*, 1973).

At present, most urologists make an allowance for voided volume and age in the interpretation of uroflowmetry results. This study has demonstrated how these results may be further influenced by abdominal straining. It is suggested that the method of voiding should be standardised by instructing patients, if possible, to avoid abdominal straining during uroflowmetry assessment. By doing this, a more reliable comparison between individuals may be made and an individual's results more accurately interpreted.

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# Response of the Canine Bladder Base during Reflex Micturition

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Summary—The response of the bladder base to filling and voiding was studied in a surgical dog model in which the bladder base was separated from the main body and closed to form a chamber. In the bladder distension phase there was a reduction in pressure in the bladder base chamber, which implies relaxation of the bladder base. In the expulsion phase the reflex bladder body activity took place with an increase in bladder base pressure, indicating contraction. Relaxation and contraction were blocked by propranolol and phentolamine respectively and both responses were abolished by trimetaphan. It was concluded that the bladder base activity in the micturition cycle is a reflex action mediated via the sympathetic nervous system.

In both pharmacological and functional terms, the urinary bladder can be divided into 2 sections—the bladder body and bladder base (El-Badawi and Schenk, 1966; Edvardsen and Setekleiv, 1968; Raezer *et al.*, 1973). Experimental findings indicate that the bladder base is involved in the internal sphincter mechanism (Hutch, 1965; Tanagho and Miller, 1970; Nergardh, 1975), but the functional importance of the base during the voiding cycle remains controversial (Edvardsen, 1968; Nergardh, 1975). Although the bladder base, including the trigonal structure and other smooth muscle fibres below the level of the ureteric orifices, has been extensively studied, relatively few *in vivo* studies have specifically involved the bladder base. It has been reported that activation of vesical afferents by bladder distension produces reflex activity in the proximal urethra (Kiruluta *et al.*, 1981). It therefore seemed worthwhile to evaluate the behaviour of the bladder base during the whole micturition cycle obtained by bladder filling. The present study used a canine model to assess the responses of the bladder base during micturition and these were recorded synchronously with those of the bladder body. In order to identify the mechanism of the bladder base responses, several autonomic agents were administered.

## Materials and Methods

Thirty-one male mongrel dogs, weighing from 8 to 15 kg, were anaesthetised with intravenous alpha-chloralose (Fluka AG, Ltd). An initial dose of 80 to 100 mg/kg was given, supplemented by small additional doses if necessary. The bladder was exposed via a suprapubic incision and the bladder base was separated from the bladder body at a level just below the ureteric openings. Great care was taken not to injure the nerves and blood vessels in this area. The 2 sections of the bladder were made watertight with a 3–0 silk ligature. The bladder was thus divided into an upper chamber, comprising the bladder body, and a lower chamber, comprising the bladder base (Fig. 1). A 10 F catheter was inserted through a stab incision in the dome of the bladder body and secured by a purse string suture. An 8 F polyethylene tube, with a side hole, was introduced into the lower chamber via the external urethral meatus. This tube was secured in position throughout the experiment by a stitch placed near the urethral meatus. In order to drain off the perfusion fluid medium that the lower chamber could not contain, an additional venting tube (6 F)

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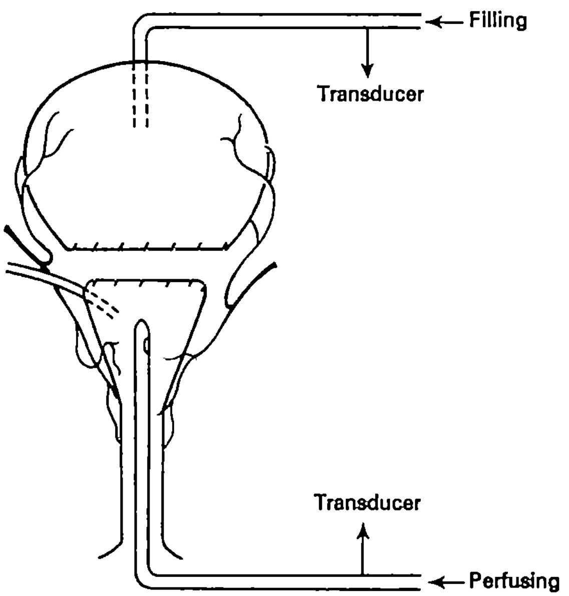

**Fig. 1** Diagrammatic representation of the experimental model.

was inserted in the bladder base chamber. The femoral artery and vein were cannulated for blood pressure monitoring and administration of drugs.

*Urodynamic studies.* Perfusion of the bladder base chamber (5 ml/min) and filling of the bladder body (20 ml/min) were carried out by syringe pumps with warm saline (38°C). The catheters used to measure the pressure changes in the 2 chambers were connected on side arms to Statham P23 pressure transducers which were coupled to a multichannel pen recorder (Model SW-III, Chongqing Meter and Instrument General Factory). After preparation of the animal, there was a 1-h delay to allow stabilisation to take place. The bladder body was evacuated. While the bladder emptying pressure was being monitored, the perfusion pressure in the bladder base chamber was recorded as a resting lower chamber pressure. The 2 chambers were then filled synchronously until a reflex detrusor contraction occurred. The pattern of changes in the lower chamber pressure was noted in relation to vesical activity during the micturition cycle.

*Pharmacological studies.* The above procedure was repeated after intravenous administration of the following drugs. Each dog served as its own control. The drugs were used in their commercially available pharmaceutical form. (1) Phentolamine mesylate 1 mg/kg was given to 8 dogs. Blockade was tested by the failure of levarterenol bitartrate 0.01 mg/kg to induce α-stimulating effects on the cardiovascular system. (2) In 8 dogs the muscarinic receptors were blocked by atropine sulphate 0.3 mg/kg. Blockade was assessed by the inability of bethanechol chloride 0.05 mg/kg to produce a powerful bladder contraction. (3) Propranolol hydrochloride 3 mg/kg was given to 7 dogs. Blockade was tested by the failure of isoproterenol hydrochloride 0.01 mg/kg to produce beta effects on the circulation. (4) The autonomic ganglia were blocked by trimetaphan camsylate (Arfonad) in 8 dogs. Because its action is not prolonged, this agent was administered at a constant intravenous infusion rate of 1 to 6 mg/min (1 mg/ml) according to blood pressure. Its efficiency was indicated by hypotension.

## Results

*Control Experiments.* The lower chamber resting pressure was constant with a mean of 12.49 ± 3.88 $cmH_2O$ (mean ± SD). With the gradual distension of the bladder body there was a reduction in pressure in the bladder base chamber in 26 of 31 dogs ($8.02 \pm 4.8$ $cmH_2O$, $n=31$, $P<0.001$). As the drop in pressure began, the volume of the bladder body in the 26 dogs was 60 to 100 ml. When this pressure had fallen to a certain degree, no further drop was observed irrespective of the extent of upper chamber filling. In the other 5 animals there was little decrease in the lower chamber pressure. During the voiding phase in all 31 dogs there was a marked pressure rise in the bladder base chamber which slightly preceded the bladder pressure increase of reflex detrusor contraction (Fig. 2).

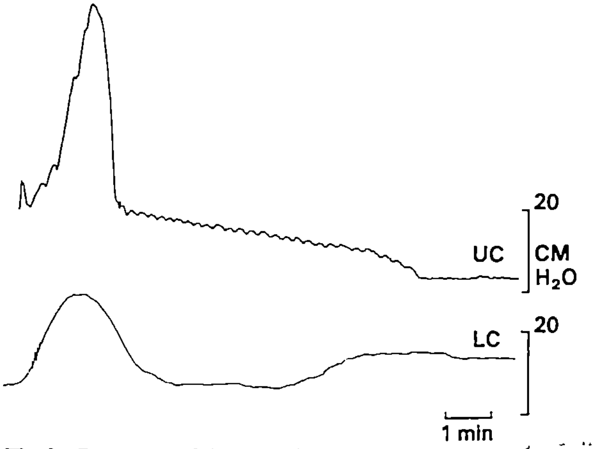

**Fig. 2** Responses of the lower (bladder base) chamber (LC) to filling and reflex contraction of the upper (bladder body) chamber (UC) in the dog. Filling had stopped when micturition occurred.

*Pharmacological experiments*

*Effect of propranolol.* No change in the lower chamber resting pressure was observed, but the relaxation response of the bladder base to vesical distension was obviously blocked. In the expulsion phase, the bladder base pressure increased even though the beta-adrenergic receptors were blocked (Fig. 3).

*Effect of phentolamine.* A reduction in the lower chamber resting pressure was observed. With filling of the bladder body a marked reduction in bladder base pressure could still be demonstrated, although the pressure rise at micturition was abolished following administration of phentolamine (Fig. 4).

*Effect of trimetaphan.* After administration of this autonomic ganglia blocker, the lower chamber resting pressure was considerably reduced. The response of reflex detrusor contraction to bladder filling was abolished and the bladder body accommodated a higher fluid volume. No changes were seen in the lower chamber pressure during the voiding cycle (Fig. 5).

*Effect of atropine.* Following blockade of the muscarinic receptors, the lower chamber resting pressure remained unchanged. The responses of the bladder base in the 2 phases of micturition were not affected to any significant degree (Fig. 6). It was shown that the contractile response of the

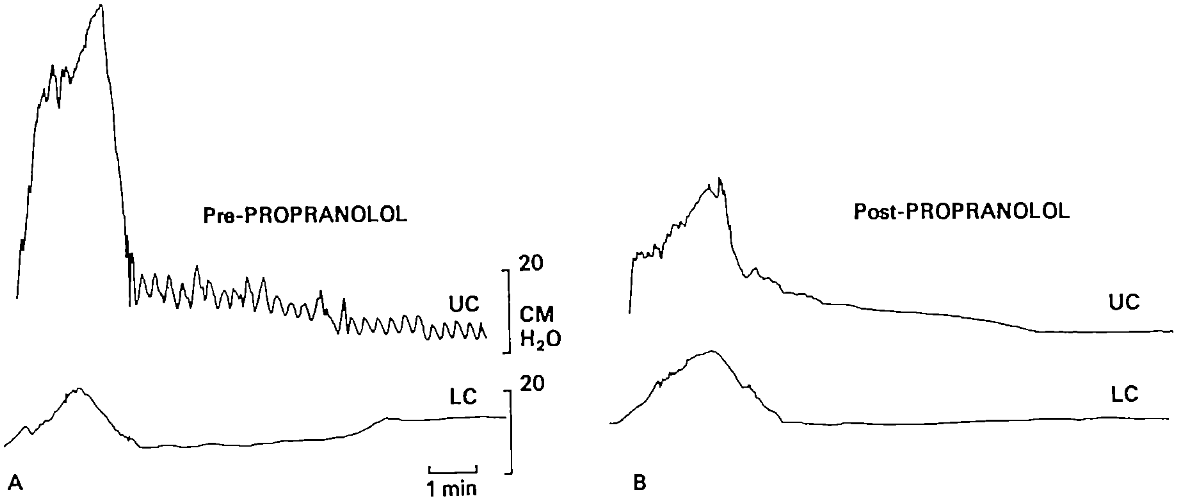

**Fig. 3** Responses of the bladder base (LC) to distension and contraction of the bladder body (UC) before (A) and after (B) administration of 3 mg propranolol hydrochloride/kg body weight Propranolol blocked the relaxation response of the bladder base.

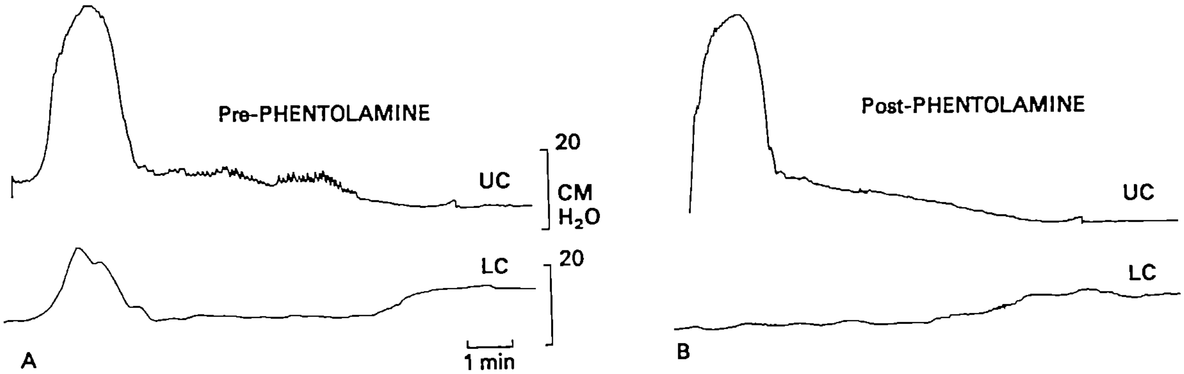

**Fig. 4** Response of the bladder base (LC) in the phases of micturition obtained by filling of the bladder body (UC) before (A) and after (B) intravenous infusion of 1 mg/kg phentolamine mesylate, which blocked the contractile response in the bladder base at voiding.

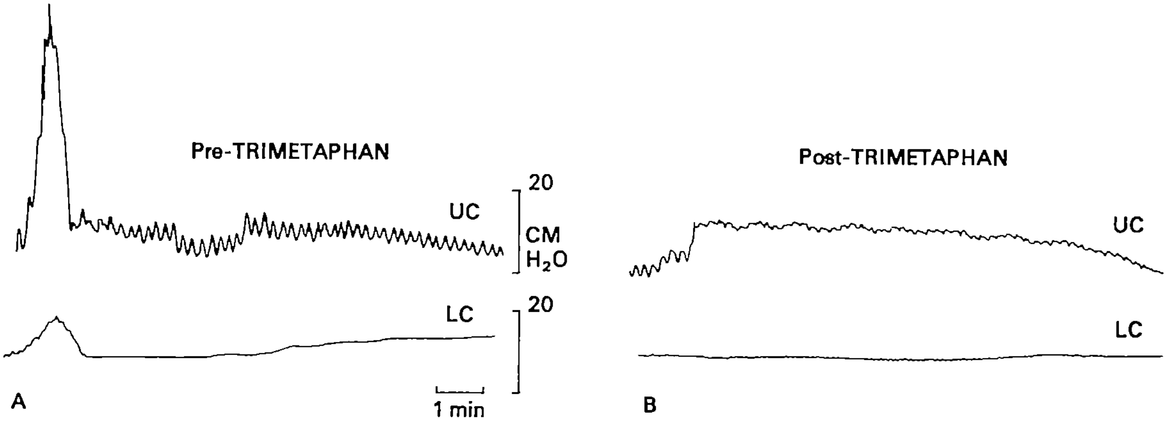

**Fig. 5** Responses of the bladder base (LC) in the voiding cycle were blocked by trimetaphan (A) Filling stopped when the volume of the bladder body (UC) exceeded 250 ml

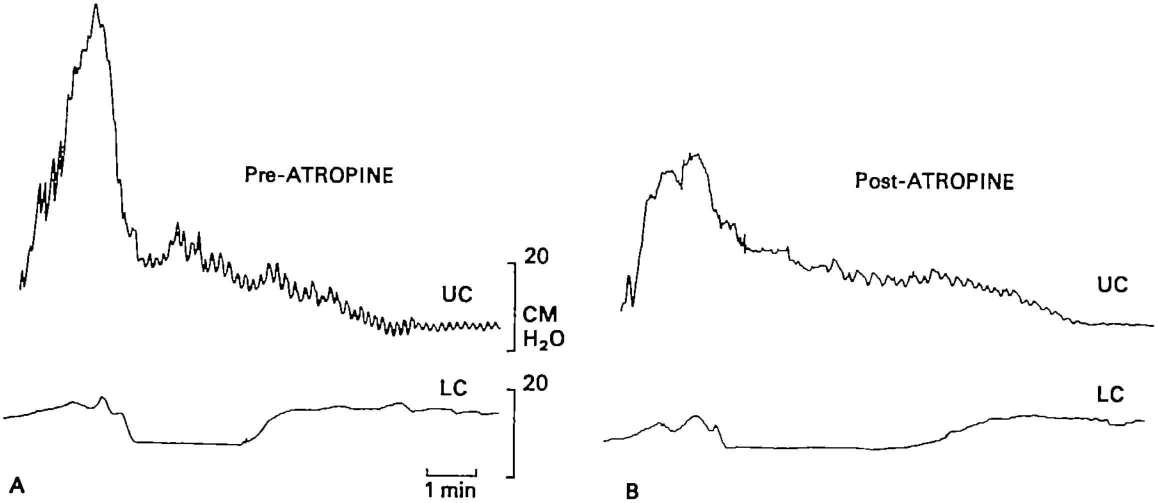

**Fig. 6** Responses of the bladder base (LC) to bladder body (UC) filling were similar before (A) and after (B) administration of atropine sulphate (0.3 mg/kg).

bladder induced by vesical filling was reduced, but not obliterated, by atropine.

## Discussion

The dog was chosen as the experimental animal in the present study because both the trigone and the rest of the canine bladder base are neuromorphologically indistinguishable (El-Badawi and Schenk, 1966; Raezer *et al.*, 1973). Alpha chloralose does not suppress the micturition reflex and it is therefore a suitable anaesthetic for such studies. Our experience indicates that in the dog, chloralose produces long-lasting, stable anaesthesia and anaesthetic induction with barbiturates or halothane, which can depress micturition reflex responses (Doyle and Brisco, 1976), is not required. We used a modification of the model described by Kiruluta *et al.* (1981), with a single separation performed at a level just below the ureteric orifices. This division eliminates muscular continuity and the possible influence of ureters on the bladder base. In 4 preliminary experiments, in which the bladder base was closed without a vent, a constant rise in perfusion pressure in the lower chamber was seen. At this point, saline was running out through the urethra around the tube and it was impossible to assess pressure changes in the lower chamber (Fig. 7).

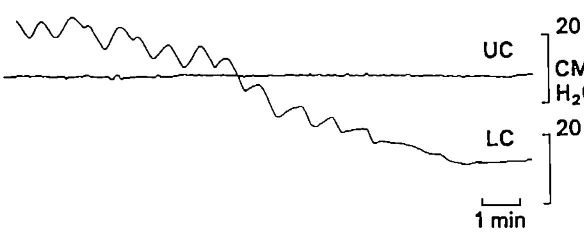

**Fig. 7** Without an open venting tube in the lower chamber, a constant rise in pressure was shown in the bladder base chamber (LC) while the bladder body was empty.

Our control experiments revealed that the behaviour of the bladder base pressure in the micturition cycle follows a regular pattern. During the collecting phase there is a gradual drop in lower chamber pressure, which indicates relaxation of the bladder base. In the expulsion phase the reflex bladder body contraction occurs with a marked rise in lower chamber pressure which implies active contraction of the bladder base. Following anatomical and cineradiographic studies of the lower urinary tract, Hutch (1965) and Tanagho and Miller (1970) concluded that the activity of the bladder base was passive and conformed to that of detrusor muscle loops of the bladder body. In our study, the responses of the bladder base during the voiding cycle were not affected despite muscular separation but they were abolished by ganglionic blocking agents. These results provides objective evidence that the function of the bladder base is mediated largely via autonomic ganglia and involves nervous reflex activity.

*In vitro* studies (Raezer *et al.*, 1973; Nergardh, 1975) have shown that stimulation of cholinergic receptor function with acetylcholine produces a contraction of the bladder base muscle in the dog. However, our results failed to demonstrate that muscarinic receptors were involved to any significant degree during the reflex rise and fall in lower chamber pressure. However, we did observe that the relaxation response of the bladder base to distension was sensitive to propranolol and the contractile response at micturition was blocked by phentolamine. It would therefore seem that the reflexes involved in the changes in bladder base pressure are mediated through the potentiation of beta- and alpha-adrenergic receptors respectively. It has been established that the bladder base in the dog possesses abundant adrenergic nerve endings and α-adrenoceptors, stimulation of which results in contraction (Dhasmana *et al.*, 1970). Beta-adrenergic receptors have also been identified in the canine bladder base, where their activation promotes relaxation (Gregg *et al.*, 1970; Raezer *et al.*, 1973). Learmonth (1931) and DeGroat and Lalley (1972) noted that bladder filling elicited reflex impulses in sympathetic efferents to the bladder as well as sympathetic-mediated inhibition of detrusor smooth muscle. In addition to confirming these findings, Edvardsen and Setekleiv (1968) and Satchell and Vaughan (1988) observed a sharp increase in sympathetic efferent activity at the time of spontaneous voiding. It therefore appears that control of the bladder base during the micturition cycle is regulated by the sympathetic nervous system.

It seems paradoxical that in the same bladder base the relaxation activated by β-adrenoceptors and the contraction controlled via α-adrenoceptors occur in the collecting and expulsion phases respectively as the activation of both α- and β-adrenergic receptors is mediated by the sympathetic nerve. Using transmural electric field stimulation of muscle strips taken from the bladder base in both man and the pig, Klarskov *et al.* (1983) found that frequencies of 5 Hz induced the most pronounced relaxation; this was inhibited by propranolol, whereas frequencies from 20 to 30 Hz produced contraction, which was diminished by phentolamine. During *in vivo* experiments, Edvardsen (1968) and Kleeman (1970) noted contraction at the bladder base in both dog and cat on sympathetic nerve stimulation. On the other hand, using the same animals and methods, Sigg and Sig (1964) and Homsy (1967) observed no contraction at the bladder base. This may be explained by the different frequencies and intensities of stimuli used in their experiments. All of these findings suggest that the activity of the bladder base is predominantly associated with the characteristics of sympathetic firing itself. Moreover, it has been discovered that alpha versus beta receptor sites are preferentially activated as a function of muscle cell length (Benson *et al.*, 1975), concentration of transmitter chemical (Salimi *et al.*, 1969) and status of central innervation (Nergardh, 1974). It is therefore likely that dual adrenergic receptors in the bladder base operate in harmony under physiological conditions *in vivo*. The mechanisms by which α- and β-adrenoceptors are co-ordinated at the bladder base during the voiding cylce have yet to be explained.

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# Haematuria Frequency Syndrome in Patients with Positive HIV Serology: Observations in Zambia

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Summary—Observations are presented on 9 patients recently treated in the University Teaching Hospital, Lusaka, Zambia, for painful urinary frequency, suprapubic pain and microscopic and/or macroscopic haematuria without any demonstrable urinary tract infection. At cystoscopy the bladder mucosa of all patients depicted a highly characteristic, uniformly congested appearance with no demonstrable ulcers; there was no significant reduction in bladder capacity. The histological appearance was essentially non-specific in type with an apparent resemblance to that of interstitial cystitis; mast cells were, however, absent in all specimens. An important feature common to all patients was an associated HIV infection; cytochemistry of the bladder tissue did not reveal an associated cytomegalovirus cystitis. No such case was observed in Zambia prior to the advent of HIV infection and the phenomenon was observed only in seropositive patients. It has been suggested that the virus is likely to be associated with the genesis of the bladder symptoms. The natural history of the disorder, its incidence among the seropositive individuals and its pathogenesis remain unclear.

During the early part of 1986 a 45-year-old male attended the urology clinic of the University Teaching Hospital, Lusaka, with marked diurnal and nocturnal urinary frequency, uralgia, suprapubic pain and persistent microscopic haematuria of 6 months' duration. The urine was sterile on repeated culture; culture for TB was also negative. Cystoscopic examination revealed a diffusely congested bladder mucosa. Bladder biopsy was reported as showing features of 'non-specific cystitis'. The patient's symptoms failed to respond to various antibiotics, including an empirical course of antituberculous drugs. Subsequently the patient absconded from follow-up; his urinary disorders remained undiagnosed. More patients continued to be seen in the urology out-patient clinic with identical urinary symptoms and cystoscopic appearance. Their management remained unsatisfactory and they were described as cases of idiopathic haematuria frequency syndrome.

Starting in early 1988, all such cases were subjected to an elaborate clinicopathological evaluation with a view to objectively outlining the characteristic features of what appeared to be a relatively new urological disorder in Zambia. The following is an account of 9 such consecutive patients.

## Patients and Methods

The 9 Zambians (8 male, 1 female) with a mean age of 36 years (range 30–49) were seen over an 18-month period (January 1988–June 1989). All were subjected to meticulous physical examinations with emphasis on the presence of lymphadenopathy and mucocutaneous lesions. The investigations included microscopy and culture of midstream urine, culture for urinary TB, Hb, urea and electrolytes, VDRL, HIV serology, chest X-ray, intravenous urography, cystoscopy and 4 quadrant bladder biopsy.

The formalin-fixed bladder tissues were stained

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using the haematoxylin-eosin, Ziehl-Neelsen, toluidine blue methods; 5 bladder tissues were further subjected to cytochemical staining using monoclonal antibody (Dakopatts Limited) for the detection of cytomegalovirus. The subtype of the infiltrating lymphocytes was determined using cytochemistry in 1 instance.

## Results

Painful urinary frequency (D/N > 6/6) with microscopic and/or macroscopic haematuria were the dominant urological features in all patients. The suprapubic area was moderately tender in all and only 1 failed to have palpably enlarged lymph nodes (Table 1). Only 2 patients demonstrated evidence of past multidermatomal herpetiform eruptions on the trunk and 2 males had an aggressive type of venereal warts. All urine samples were initially sterile on culture and none was positive for *Mycobacterium tuberculosis* on guineapig inoculation. Biochemical parameters of renal function and urograms were normal in all patients. All demonstrated a positive HIV serology (ELISA and Western blot test); the seropositive status of 2 patients was known before their referral to the urologist. Prior to the onset of symptoms, no patient was on any medication apart from occasional antibiotics and analgesics.

At cystoscopy, under general anaesthesia, the bladder mucosa was noted to be uniformly congested with a highly characteristic reddened appearance in all patients. There was no demonstrable bladder ulcer. No significant reduction in bladder capacity was observed in any patient; the capacity ranged between 350 and 500 ml. Diffuse mucosal bleeding occurred in all patients following moderate filling of the bladder.

The histological features (Table 2) were essentially non-specific in type with intra- and subepithelial lymphocytic infiltration, diffuse suburothelial vascular dilatation and oedema (Fig.). Three patients had dead bilharzial ova in the submucosa with moderate eosinophilia.

The subepithelial lymphocytes were predominantly T cells and the intraepithelial variety comprised both subtypes. Macrophages were scanty, mast cells and cytomegalovirus were absent. The presence of cytomegalovirus was ruled out by a combination of cytochemistry and haemotoxylin-eosin methods.

A limited follow-up, averaging 11 months (range 6–16) was possible on 6 patients (Table 1); improvement in the urinary symptoms was not observed and deterioration was noted in 2 cases. Repeat urine culture demonstrated an *Escherichia coli* infection in 2 patients. A repeat cystoscopy was possible on 5 patients; there was no alteration in

**Table 1** Salient Features of 9 Patients

| *Patient no.* | *Age, sex* | *Duration of bladder symptoms (months)* | *Type of haematuria* | *Enlarged nodes* | *Cutaneous lesions* | *Repeat urine culture (interval)* | *Repeat cystoscopy (interval)* | *Follow-up (months)* |
|---|---|---|---|---|---|---|---|---|
| 1 (CM) | 49M | 4 | Terminal | Axillary, femoral | None | Not done | Not done | Nil |
| 2 (MC)* | 49M | 6 | Terminal | Generalised | Healed herpes | *E coli* (6 months) | Reduced bladder capacity (14 months) | 16 |
| 3 (HM) | 38F | 3 | Microscopic | Generalised | Healed herpes | Sterile (8 months) | Not done | 10 |
| 4 (RM) | 29M | 4 | Microscopic | Axillary | None | Not done | Not done | Nil |
| 5 (RL) | 40M | 6 | Microscopic | None | None | Not done | Not done | Nil |
| 6 (MH) | 38M | 2 | Terminal and total | Generalised | Penile warts | Sterile (6 months) | Unchanged (5 months) | 6 |
| 7 (WS) | 40M | 6 | Microscopic | Generalised | None | *E coli* (10 months) | Unchanged (10 months) | 14 |
| 8 (MK) | 30M | 3 | Terminal | Axillary, femoral | Penile and perineal warts | Sterile (12 months) | Unchanged (12 months) | 12 |
| 9 (EL)† | 31M | 6 | Terminal and total | Generalised | None | Sterile (12 months) | Unchanged (12 months) | 12 |

*Has developed AIDS
†Has since died, cause of death not known.

**Table 2** Summary of Bladder Biopsy Findings

| *Patient* | *Ero* | *Epih* | *Iel* | *Sepi infl* | *If* | *Vad* | *Oed* | *Sch* | *Eos* |
|---|---|---|---|---|---|---|---|---|---|
| CM | – | – | – | + | – | +++ | + | + | + |
| MC | – | + | + | ++ | – | ++ | + | – | – |
| HM | – | + | + | ++ | – | ++ | + | – | – |
| RM | + | – | + | ++ | – | +++ | ++ | + | + |
| RL | – | – | + | + | – | ++ | + | – | – |
| MH | + | – | + | ++ | – | ++ | + | + | + |
| WS | – | – | – | ++ | – | ++ | + | – | – |
| MK | + | – | + | ++ | – | ++ | + | – | – |
| EL | – | – | + | + | – | ++ | + | – | – |

Ero—Epithelial erosion.
Epih—epithelial hyperplasia.
Iel—intra-epithelial lymphocytes.
Sepi infl—Subepithelial inflammatory cells (mainly lymphocytes).
If—lymphoid follicles.
Vad—vascular dilatation.
Oed—oedema.
Sch—schistosomiasis.
Eos—Eosinophilia.

the mucosal appearance and bladder capacity measured under anaesthesia was noted to have reduced (<250 ml) in 1 patient. One patient died within a year and another is known to have developed AIDS.

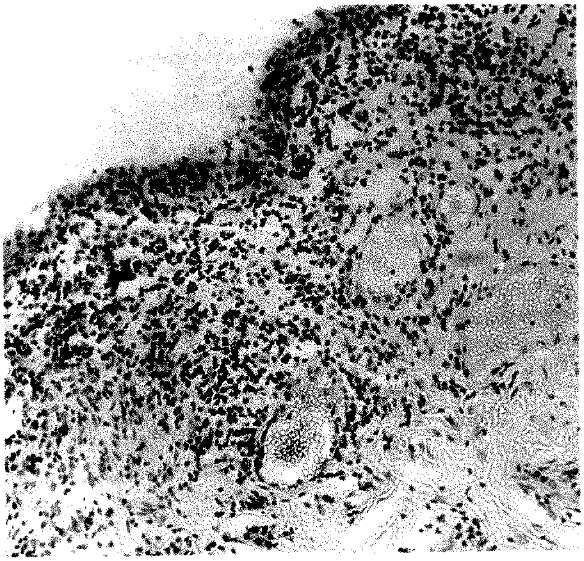

**Figure** Mucosal biopsy of the bladder showing chronic cellular infiltrate, oedema and a marked suburothelial vascular dilatation (H and E × 250).

## Discussion

The above patients represent a type of bladder disorder hitherto not seen in Zambia. All patients were characterised by the presence of well defined clinical features and a distinctive cystoscopic appearance. The aetiology remains conjectural, while very little is known about the natural history of this syndrome. The presence of a sterile urine on initial presentation in all cases precludes bacteria as an aetiological agent; culture for tuberculosis was also negative and the histology bore no resemblance to a tuberculous pathology. Similarly, the presence of inactive bilharziasis in some of the bladder specimens is more a reflection of the endemicity of the parasites in Zambia and thus has no aetiological significance since the cystoscopic appearance and pattern of cellular response are highly atypical of bilharzial cystitis. On the basis of the histological appearance it could be suggested that the bladder disorder is a variant of interstitial cystitis; the absence of mast cells, however, negates such an assumption. Moreover, more than 90% of the affected patients were male. The fact that only 1 case of interstitial cystitis has been seen by one of the authors (B.E.) in the University Teaching Hospital during the preceding 10 years exemplifies its rarity in Zambia.

An important factor common to all 9 patients was an associated HIV infection; one can only speculate on the possible role of the virus in the genesis of the vesical pathology. The fact that no such case was observed in Zambia prior to the advent of HIV infection and that none of the affected patients was seronegative lends credence to a probable causal role of the virus. Any consideration as to the possible mode of action of the virus on the bladder, however, is beyond the scope of the present report.

A small proportion of AIDS patients develop cytomegalovirus cystitis (Reichert *et al.*, 1983; Lucas *et al.*, 1989; there was no histological evidence of associated cytomegalovirus infection in any of our patients. Moreover, none of these patients was clinically considered to be suffering from AIDS during their initial presentation. Entirely on the basis of clinical features, all but 1 belonged to Walter Reed stage 2 or 3 (Redfield *et al.*, 1986).

The natural history of HIV-related cystitis is far from clear; whether the development of a contracted bladder, as observed in a single case with the longest follow-up, is a pointer to the pattern of progression of this disorder remains to be seen. Similarly, the proportion of seropositive individuals likely to develop such bladder symptoms is far from clear. Miles *et al.* (1989), however, in a retrospective study of 120 patients with either AIDS or its related complex, noted 2% who presented with gross haematuria; none of these patients had a bladder biopsy.

Urologists should be aware of this association; one is likely to learn about its global prevalence only by performing HIV serology in all patients with intractable cystitis and this highly characteristic cystoscopic appearance.

## Acknowledgements

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# Artificial Urinary Sphincters around Intestinal Segments—Are they Safe?

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Summary—Artificial urinary sphincters (AUS) were implanted around intestinal segments to achieve urinary continence in 8 patients and faecal continence in 1. In 6 patients the cuff was placed around the lower end of the cystoplasty following bladder neck (5) or urethral (1) erosion. Four are completely dry, 1 on self-intermittent catheterisation (SIC). One has mild stress incontinence. In 1 patient the cuff eroded at 8 months.

Two patients had cuffs implanted parastomally to create continent diversion. One is satisfactory on SIC and the other had her AUS explanted because of life-threatening metabolic acidosis. The rectal cuff was explanted because of faecal impaction above the cuff.

As an absolute last resort, placing an AUS round a cystoplasty appears little more hazardous than round bladder neck. The use of the AUS for continent diversion has not been pursued because of reliable techniques of non-prosthetic continent diversion. The current model of the AUS is unsuitable for the treatment of faecal incontinence.

Since their introduction by Scott *et al.* (1973), artificial sphincters have been successful in the treatment of urinary incontinence due to sphincter weakness. Improvements in design and quality control over the years have made the AUS extremely (though not totally) mechanically reliable.

The majority of sphincters implanted on this unit are in patients with neuropathy and since the bladder is almost always reconstructed, it has been shown that the AUS may safely be implanted at the same time as the cystoplasty (Stephenson and Mundy, 1985; Nurse and Mundy, 1988).

The successful use of the AUS in urology has prompted some general surgeons to contemplate its use in faecal incontinence; the first successful implantation of such a sphincter was described in a patient with anal incontinence and myasthenia gravis (Christiansen and Lorentzen, 1987).

## Patients and Methods

Between 1984 and 1988, 8 patients aged between 17 and 34 years underwent urological reconstructive surgery with insertion of an AUS around an intestinal segment to achieve urinary continence. In addition, a 13-year-old female with sacral agenesis who already had a satisfactory cystoplasty and bladder neck sphincter had an AUS implanted around the rectum (Fig. 1). Apart from this child, the patients fell into 2 groups. Six patients had previously undergone reconstruction of the bladder and AUS placed at the bladder neck (5) or distal bulbar urethra (1). Clinical data on these patients are shown in Table 1. Erosion of the cuff had occurred in each patient at least once and the cuff was moved to the lower end of the cystoplasty in an omental "sandwich" (omentum placed both under and over the cuff) except in the patient who had undergone cystectomy and partial urethrectomy, where it was placed round the ileal segment bridging the gap (Fig. 2). All patients had low pressure reservoirs (51–60 cm $H_2O$) to minimise the risk of erosion. Two patients subsequently needed smaller cuffs, probably because of inappropriately large cuffs initially, and 1 patient needed a higher pressure reservoir to maintain continence.

The second group consisted of 2 non-walking spina bifida patients, both with unsatisfactory

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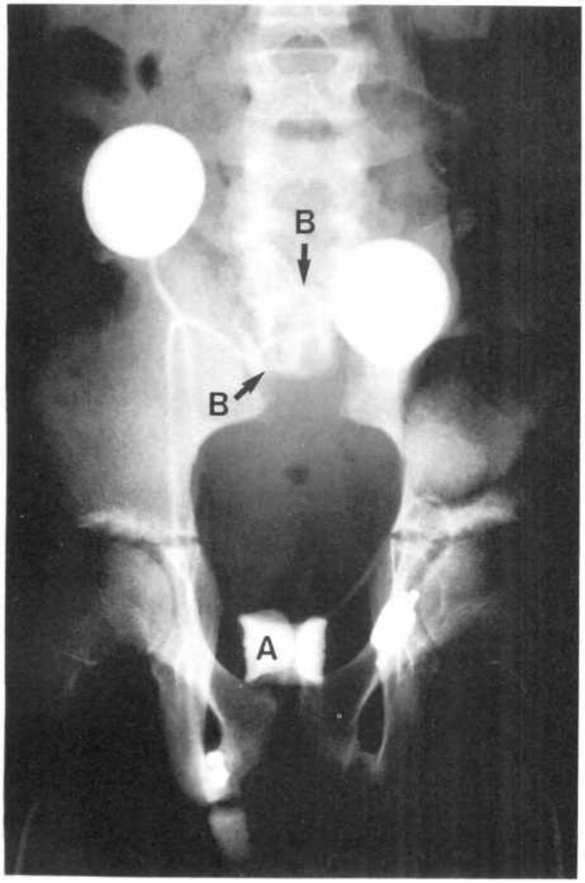

**Fig. 1** Plain radiograph showing AS 792™ AUS with cuff (A) around bladder neck and AS 800™ AUS with deactivated cuff (B) around rectum.

surface diversions and deteriorating upper tracts. In both cases a continent diversion was created using caecum and implanting the AUS cuff subcutaneously parastomally (Fig. 3). One was continent with the cuff alone and the other required activation.

## Results

The main group with cuffs round their cystoplasties have done well (Table 2) with 1 exception, a patient whose cuff eroded at 8 months but who is now dry on SIC. Four are completely dry, 1 on SIC; the boy with the cuff round the ileal "bridge" has mild stress incontinence and we have been reluctant to insert a higher pressure reservoir.

Of the 2 patients with cuffs round their stomas, 1 was explanted because of life-threatening metabolic acidosis and the other remains continent on SIC, though his first cuff had to be changed when the cuff tubing eroded through the skin.

All of the patients with deteriorating upper tracts have stabilised.

The girl with sphincter round the rectum had the device explanted at 1 month as she became faecally impacted above the cuff and required emergency colostomy. With the the value of hindsight it was clearly inappropriate to implant a device in a neuropathic patient with a sluggish colon and chronic constipation.

## Discussion

A number of reports have been published on the use of the AUS both in animals and humans.

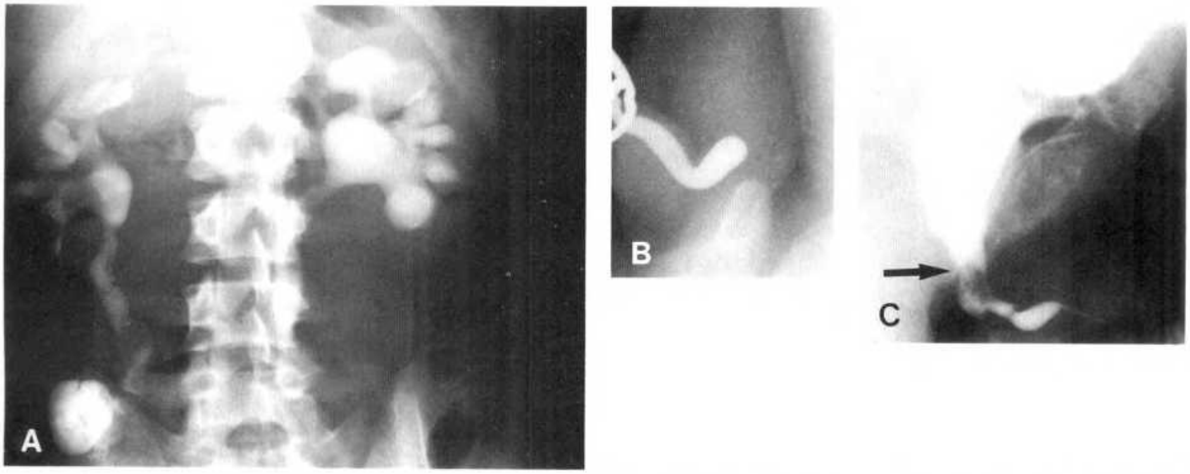

**Fig. 2** Composite radiograph showing (A) bilateral hydronephrosis, (B) ascending urethrogram to mid-bulb, (C) completed cystoplasty with ileal bridge. Arrow marks site of AUS cuff insertion.

**Table 1** Clinical Details. AUS Cuffs round Cystoplasties

| *Patient* | *Diagnosis* | *Upper tracts* | *Reconstruction* | *Follow-up (months)* |
|---|---|---|---|---|
| F22 | Closed ectopia vesicae. Incontinent | Deteriorating | Cystoplasty + AUS round reconstructed bladder neck-erosion—cuff round cystoplasty | 31 |
| F17 | Ectopia vesicae. Ureterosigmoidostomy (+tumour) | Deteriorating | Sigmoid colectomy. Cystoplasty, vaginoplasty + cuff round bladder neck—uncovered vaginally—cuff round cystoplasty | 11 |
| F25 | Spina bifida (ileal loop) | Stable | Undiversion-clam and AUS-erosion × 2—cuff round cystoplasty | 12 |
| F28 | Traumatic destruction of rhabdosphincter. Incontinent | Stable | Cystoplasty + AUS erosion at 4 years—cuff round cystoplasty | 10 |
| M17 | Rhabdomyosarcoma. Cystectomy + partial urethrectomy (ileal loop) | Deteriorating | Cystoplasty + ileal "bridge" + bulbar AUS-erosion—cuff round ileal "bridge" | 16 |
| M34 | Osteosarcoma. Surgery + radical radiotherapy. Incontinent | Deteriorating | Cystoplasty + AUS round irradiated bladder neck-erosion—cuff round cystoplasty | 9 |

Engelmann *et al.* (1985) evaluated pressure flow studies, microangiography and histopathological changes following implantation of the AUS round isolated bowel loops in rabbits. Fibrous capsule formation occurred regularly round the cuff (as it does in humans) but did not impair function when the device was regularly cycled. Mucosal and lymphoid tissue atrophy was noted but (more importantly) the muscularis remained intact without loss of vasculature or cell mass. Bowel necrosis occurred most commonly with high cuff pressures of 100 cm of water.

Animal models have been used to assess the AUS around intact bowel segments at both ends of the

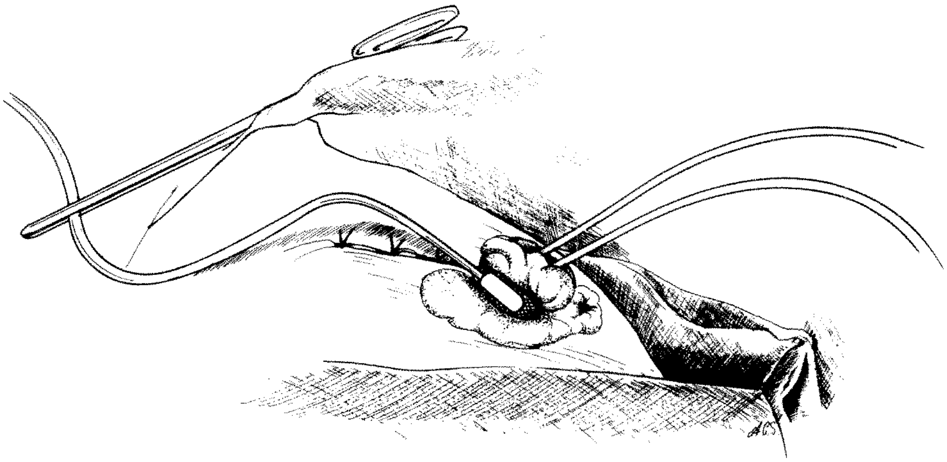

**Fig. 3** AUS cuff implanted subcutaneously around stoma.

**Table 2** Results AUS Cuffs round Cystoplasties

| *Patient* | *Diagnosis* | *Outcome of surgery* | *Upper tracts* |
|---|---|---|---|
| F22 | Ectopia vesicae | Continent, voiding with activation AUS | Deteriorating<br>↓<br>stable |
| F17 | Ectopia vesicae | Continent, voiding with SIC | Deteriorating<br>↓<br>stable |
| F25 | Spina bifida | Continent, voiding with SIC for 8 months—erosion | Stable<br>↓<br>stable |
| F28 | Traumatic destruction of rhabdosphincter | Continent, voiding with activation AUS | Stable<br>↓<br>stable |
| M17 | Rhabdsarcoma | Mild stress incontinence, voiding with activation AUS | Deteriorating<br>↓<br>stable |
| M34 | Osteosarcoma. Surgery + radiotherapy | Continent, voiding with activation AUS | Deteriorating<br>↓<br>stable |

gastrointestinal tract. Miskowiak *et al.* (1987) implanted the AUS round the subphrenic oesophagus in 6 pigs. The oesophagus tolerated cuff pressures of 28 to 95 cm of water. However, dysphagia occurred in pigs kept alive for more than 1 month due to malfunction of the device because of surrounding fibrosis.

A dog model has been used to evaluate the AUS to preserve anal continence (Sofia *et al.*, 1988). Continence was achieved in 7 of 15 animals, but complications including infection, device extrusion and malfunction occurred in the others.

In the human, the first AUS placed round bowel to maintain urinary continence (following undiversion) was reported by Light *et al.* (1983). The main indication has been in patients with exstrophy. Burbige *et al.* (1987) reported 9 such patients, all but 1 of whom were initially continent, but 8 became incontinent 6 to 10 months post-operatively because of attenuation and shrinkage of the bowel under the cuff. The one patient in whom it did not occur had omentum interposed between the cuff and the bowel. Thus it seems clear from this and our series that the omental sandwich offers some protection against shrinkage and erosion.

It is noteworthy that in our overall series of implanting the AUS we have moved the cuff to the lower end of the cystoplasty in 1 of 80 neuropathic patients (though there have been other erosions), but in 2 of 3 exstrophies, and in the only irradiated bladder so reconstructed. The Guy's Hospital experience of implanting the AUS round the irradiated bladder neck precludes its use in this situation (Mundy, personal communication). Thus all but 1 of the main group reconstructed had poor tissues where the cuff was originally placed, but all 5 had over-riding medical indications for surgical intervention, usually deteriorating renal function. At the moment, as an absolute last resort, placing a cuff round a cystoplasty appears little more hazardous than round bladder neck.

We have not pursued the use of the AUS for continent diversion because of the development of fairly reliable techniques of non-prosthetic continent diversion.

The use of the current model of the AUS or some modification thereof for faecal incontinence is an important issue.

In our own practice with a large group of teenage myelodysplastic patients, faecal leakage is often the central issue, especially if urinary continence has been achieved. Results elsewhere (Christiansen and Lorentzen, 1987) have been very disappointing and it seems certain that the device would need modification to be suitable. Even then, in the myelodysplastic patient it would conceptually be necessary to perform a total colectomy and create a small bowel pouch anastomosed to the rectum above a sphincter; this would be a major undertaking and hazardous to a pre-existing urinary sphincter if present. The future here thus seems uncertain.

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# Artificial Urinary Sphincter Insertion in Congenital Neuropathic Bladder

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Summary—A series of 44 patients with neuropathic bladder dysfunction due to congenital myelodysplasia underwent implantation of an artificial urinary sphincter (AUS); in 26 patients a reconstructive procedure was performed at the same time. Five patients who initially had AUS implantation alone developed detrusor hyper-reflexia and required a clam cystoplasty.

Forty patients (90%) are continent, 2 are occasionally damp and 2 are wet and awaiting further surgery; 66% of patients who underwent AUS insertion and reconstruction were found to have significant residual urine and they perform intermittent self-catheterisation (ISC).

In patients with a good bladder capacity and normal compliance and detrusor hyper-reflexia controlled by anticholinergic drugs, cystoplasty is not necessary at the time of AUS insertion.

Since the introduction of the first AUS by Scott and Bradley in 1973, significant advances have been made in the reliability of the device and the AUS now has an established role in the treatment of refractory stress incontinence. Urinary incontinence in patients with congenital neuropathic bladders results from either sphincter weakness, detrusor hyper-reflexia or hypocompliance or a combination of both. In patients with intermediate type bladders (Rickwood *et al.*, 1982; Mundy *et al.*, 1985), it is now common practice to perform an augmentation or substitution cystoplasty at the time of sphincter insertion.

We report our experience with the AUS and cystoplasty in patients with congenital neuropathic bladder.

## Patients and Methods

Between January 1984 and December 1989, AUS insertion was performed in 44 patients with congenital neuropathic bladder, the majority of whom had myelomeningocele (Table 1). There were 37 males and 7 females with an age range of 11 to 43 years (mean 21). Five patients were confined to wheelchairs and the remainder were ambulatory with or without a walking aid. All patients underwent pre-operative video-urodynamic studies to confirm the presence of genuine stress incontinence and to assess their bladder capacity, degree of hyper-reflexia (if present), bladder compliance and the presence of sphincter dyssynergia; 14 patients had acontractile bladders and 30 had intermediate type bladder activity (Rickwood *et al.*, 1982). In 35 male patients a sphincterotomy was performed prior to AUS insertion to facilitate bladder emptying. Those patients with genuine stress incontinence, a low pressure bladder and a good bladder capacity (>350 ml) had an AUS insertion alone. Combined AUS insertion and cystoplasty were performed in patients with genuine stress incontinence, a small capacity bladder exhibiting detrusor hyper-reflexia and/or low compliance defined as an end fill pressure of $>30$ cm/$H_2O$ on medium fill cystometry.

Eighteen patients (14 acontractile and 4 intermediate type bladders) had AUS insertion alone; 22 patients with intermediate type bladders had AUS insertion in association with either a cystoplasty or bladder augmentation and 4 had an undiversion and AUS insertion. Eight patients with hydronephrosis and significant detrusor hyper-

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Read at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

**Table 1** Aetiology

| | *No. of patients* |
|---|---|
| Spina bifida | 38 |
| Lipoma of cauda equina | 4 |
| Sacral agenesis | 2 |
| Total | 44 |

reflexia had a cystoplasty in association with AUS insertion.

Patients with indwelling catheters had their catheters removed at least 3 days pre-operatively and were given prophylactic antibiotics in addition to antiseptic baths. Those undergoing AUS insertion and a reconstructive procedure had an orthograde bowel preparation. All patients learnt ISC prior to the procedure.

The operative details have been described in detail elsewhere (Scott *et al.*, 1981). Early in the series the AUS cuff was placed around the bladder neck in the male and around the upper urethra in the female. With increasing experience the AUS cuff was placed around the membranous urethra. In patients undergoing a cystoplasty the AUS cuff was inserted at the time of cystoplasty and the AUS balloon and control valve were inserted at a second procedure approximately 6 weeks later. Eight patients had an AMS 792 system inserted, the remainder the AMS 800. The type of cystoplasty was dictated by the patients' bladder capacity, degree of hyper-reflexia and the patients' shape (Table 2).

## Results

Forty patients (90%) are continent both day and night; 2 are damp but leak only on maximal exertion or when excited. Two patients are currently wet and await a further procedure. In eighteen of 27 patients (66%) who underwent a bladder augmentation and AUS insertion the residual urine exceeds 150 ml and they perform ISC.

**Table 2** Operative Procedures

| | |
|---|---|
| AUS alone | 18 |
| AUS + clam cystoplasty | 9 |
| AUS + augmentation | 13 |
| AUS + undiversion | 4 |
| Total | 44 |

**Table 3** Complications

| | |
|---|---|
| Erosion | 3 |
| Infection | 2 |
| Kink | 2 |
| System leakage | 4 |
| Pump failure | 1 |
| Stress leakage | 1 |
| Other | 2 |

Following AUS insertion, 5 patients developed detrusor hyper-reflexia and incontinence refractory to oral oxybutinin therapy. All underwent clam ileocystoplasty and are currently continent.

The complications are shown in Table 3. Three patients presented with cuff erosions necessitating removal of the AUS. Two patients, both of whom had a clam cystoplasty, developed infected sphincters requiring removal of the AUS; 1 of these patients had a second AUS which also became infected. Overall, 36% of patients required a further operation on one or more occasion. In total, 56 sphincters have been inserted into 44 patients.

Renal function has remained unchanged in 7 of the 8 patients with hydronephrosis pre-operatively. In 1 patient, renal function has deteriorated and this patient is currently on renal dialysis.

## Discussion

Augmentation cystoplasty has become an established treatment in the management of patients with a small capacity, low compliant bladder. The decision to perform a cystoplasty at the time of AUS insertion must be based on a thorough preoperative urodynamic assessment as the long-term consequences of cystoplasty have yet to be established. Stress leakage may occur early in the filling phase of cystometry, making it difficult to obtain an accurate assessment of bladder capacity and detrusor hyper-reflexia. Occlusion of the bladder neck with a catheter may prevent early stress leakage and unmask detrusor hyper-reflexia and/or low compliance. In myelodysplastic patients with genuine stress incontinence, a good bladder capacity and normal compliance, augmentation cystoplasty is unnecessary at the time of AUS insertion.

Five of the 30 patients who initially had an AUS insertion alone subsequently developed incontinence due to detrusor hyper-reflexia; 4 of these patients had acontractile bladders on pre-operative videocystometry and 1 had intermediate type bladder activity. There are 3 possible explanations for this occurrence. Firstly, the presence of hyper-reflexia may not be recognised at the time of cystometry due to underfilling of the bladder. Secondly, pubertal changes in bladder behaviour may occur in the male myelodysplastic patient unrelated to AUS insertion. Finally, the occlusive effect of the AUS on the urethra may alter bladder behaviour and provoke hyper-reflexia.

A significant number of complications required re-operation (36%), which accords with the findings in other series (Nurse and Mundy, 1988). Four of the 8 patients with the AMS 792 system developed device-related complications that required either exploration or replacement. With the introduction of the AMS 800 series and its modifications, the number of sphincter-related complications has steadily decreased. The overall incidence of infection and erosion (11%) underlines the necessity of pre-operative bowel preparation, antiseptic baths and antibiotic prophylaxis. The AUS has an established role in the treatment of sphincter weakness in patients with congenital neuropathic bladder and, with persistence, continence may be achieved in 90% of patients.

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# Rationalisation of Follow-up in Patients with Non-invasive Bladder Tumours

## A Preliminary Report

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Summary—The risk of recurrence and progression in 170 patients presenting with pTa urothelial tumours of the bladder has been estimated so that follow-up can be rationalised. Patients were followed up for between 1 and 15 years, the original pathology reviewed and those with carcinoma *in situ* (CIS) or dysplasia of the background urothelium excluded. Only 5 patients progressed over the whole follow-up period, giving an overall progression rate of 3%. Solitary tumours had an annual initial recurrence risk (AIR) of 0.23 in the first year; after the first year the AIR fell to approximately 0.1 but did not fall significantly in subsequent years up to 8 years. Of the 45 patients with multiple tumours, 32 suffered recurrences within the first year (AIR 0.71). Tumour grade did not influence either recurrence or progression. The results indicate that for solitary pTa tumours, less frequent endoscopic follow-up is justified but some continued surveillance after 5 disease-free years is necessary. The estimated risk of recurrence is a useful factor to consider when planning follow-up.

In 1978, the UICC divided its 1 category for superficial transitional cell carcinoma of the bladder into 2 separate categories, Ta and T1. Under the rules for classification it was stated that there should be histological verification of the disease leading to the pTNM post-surgical classification of pTa and pT1. The pTa tumour does not invade the lamina propria, whereas the pT1 tumour extends into the lamina propria but not into the muscle layer. Chisholm *et al.* (1980) pointed out that it was not possible to assess invasion of the lamina propria at cystoscopy and suggested that staging could not be based on clinical assessment alone but must take into account histological findings. It is known that there may be substantial differences in rates of recurrence and progression in pTa and pT1 tumours (Able, 1988), yet by convention they tend to be followed up in the same way. This policy may well be resulting in some patients having to suffer unnecessarily frequent cystoscopies. The dilemma faced by urologists managing patients with superficial bladder cancer is to identify the patients with less 'aggressive' tumours in order to reduce the number of cystoscopies without risking missing recurrences and progression. In an attempt to determine the most appropriate management of patients with pTa bladder tumours we have reviewed the clinico-pathological features of 170 such patients and present a preliminary analysis.

## Patients and Methods

The records of 170 patients with pTa bladder tumours presenting to one centre for the first time between 1973 and 1987 were reviewed (Table 1).

**Table 1** Details of Patients

| *No. patients* | *170* | |
|---|---|---|
| Sex | Male 126 | Female 44 |
| Age range (years) | Male 24–88 (64 3) | Female 46–85 (66.6) |
| Mean age | 64.8 | |
| Follow-up (years) | 1–15 | |

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The pathology of the original tumour was reviewed and graded in every case by a single pathologist (D.F.R.G.). Stage and histological grade were designated according to the criteria of the UICC (1978) and Bergkvist *et al.* (1965). This grades tumours into 5 groups (G0–G4) according to defined cytological criteria; G0–G3 are applicable to non-invasive tumours. Patients were excluded if the original notes were incomplete, if the original pathology was not available, or if coexistent carcinoma *in situ* or urothelial dysplasia was identified when the pathology was reviewed. All patients had intravenous urography before cystoscopy and those with upper tract tumours were excluded from this study. The majority of patients had transurethral resections except for a few from earlier in the study who had open resections. None had intravesical chemotherapy prior to the initial recurrence and standard follow-up check cystoscopies were performed 3-monthly for the first year, 6-monthly for 2 years and yearly thereafter unless there was a recurrence. The times to first and subsequent recurrences were recorded and any progression was noted. Progression was defined as the development of muscle invasion or distant metastases.

## Results

### *Presenting Tumours*

Of the 170 patients, 125 had single and 45 had multiple tumours. A summary of tumour grades is shown in Table 2.

### *Recurrent Tumours*

Of the 170 patients, 103 (61%) developed recurrences. Of the 125 patients with single tumours, 63 had an initial recurrence during the study period and 62 remained tumour-free. In the first year after diagnosis 29 recurred, giving an annual initial recurrence risk of 0.23, while 14 patients had an initial recurrence in the second year (AIR 0.16). Thereafter the AIR remained between 0.06 to 0.19 but there was no evidence of any further reduction of AIR with increasing time up to 8 years (Fig. 1).

**Table 2** Distribution of Grades

| | *Grade* | | | | |
|---|---|---|---|---|---|
| | *G0* | *G1* | *G2* | *G3* | *Total* |
| Single | 0 | 51 | 58 | 16 | 125 |
| Multiple | 1 | 20 | 22 | 2 | 45 |

Of the 45 patients with multiple tumours, 40 recurred and 5 remained tumour-free. In the first year after diagnosis 32 recurred (AIR = 0.71) and 4 recurred in the second year (AIR 0.31) (Fig. 1). Patients presenting with multiple tumours had a significantly increased risk of developing recurrences in the first year ($P < 0.001$, $\chi^2$ test) compared with patients with single tumours (Fig. 2). There was no significant relationship between tumour grade and recurrence.

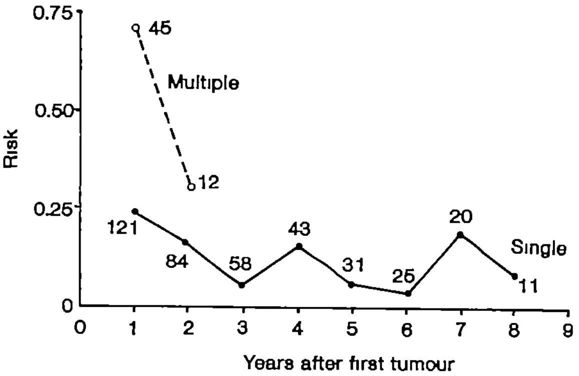

**Fig. 1** Risk of any patient developing the first recurrent tumour in any one year after diagnosis. Figures along the graph show number of patients remaining for evaluation

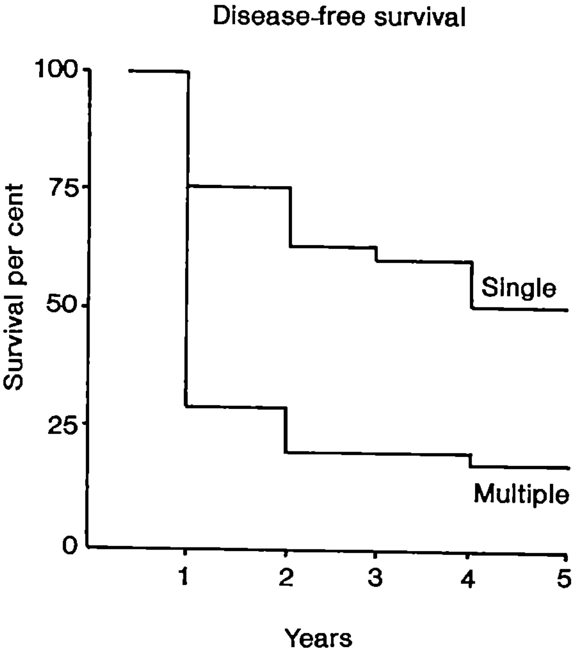

**Fig. 2** Life table comparing recurrence rate between single and multiple tumours.

### Progression and Mortality

In the single tumour group, 3 patients progressed to muscle invasion and 1 of these died from bladder cancer, giving a progression rate of 2% and a cancer mortality rate of 0.8%.

In the multiple tumour group, 2 patients progressed to muscle invasion and both went on to die from bladder cancer, giving a progression rate and cancer mortality rate of 4%. All of the patients who progressed had their initial recurrence within the first year of follow-up and this obviously has implications in planning follow-up cystoscopies. The grade of the presenting tumour was not useful in predicting which patients would progress.

## Discussion

We have studied the influence of grade and multiplicity on the disease-free survival interval of patients with pTa bladder tumours and also looked at the incidence of progression to muscle invasion. Most patients presented with single tumours and only half suffered recurrences over the complete follow-up period; in contrast, most patients with multiple tumours had suffered a recurrence within 1 year. Others have noted similar ratios of single to multiple tumours on presentation and also reported significantly increased rates of recurrence in the multiple tumour group (Cutler *et al.*, 1982; Pocock *et al.*, 1982). A recent multicentre study used multivariate methods to identify factors influencing recurrence rates of superficial bladder cancer (pTa and pT1) and found that multiple tumours on presentation and findings at first check cystoscopy were the most important prognostic indicators (Parmar *et al.*, 1989).

We did not find any relationship between tumour grade and disease recurrence or progression. At first sight this appears unusual and is apparently at variance with findings in other studies (Able *et al.*, 1988). There are 2 main reasons for this difference. Firstly, most of these previous studies have combined pTa and pT1 tumours in their analysis of histological grade. There is an excess of G3 tumours in the poor prognosis pT1 group, so unless pTa and pT1 tumours are analysed separately, then grade is not an independent variable. Secondly, no other study has excluded patients with CIS or dysplasia of the background mucosa; these patients are known to have a high risk of recurrence and progression. Unlike invasive tumours, pTa tumours can more reliably be completely resected endoscopically, so that the risk of recurrence is more likely a function of the stability of the background epithelium rather than the grade of the primary tumour itself.

This study has confirmed the low invasive potential of pTa tumours, especially if patients with CIS or dysplasia of the background epithelium are excluded. The data provide further support for separating these tumours from lamina propria invasive tumours for both analysis and for follow-up. Another important observation was that all 5 patients who progressed suffered recurrences within the first year of diagnosis. This reinforces the current policy of careful follow-up within the first year.

The study has concentrated on the time from initial resection of a bladder tumour to the first recurrence and we have calculated the AIR to provide quantitative information to enable follow-up to be planned. On the basis of our results, we propose that patients with solitary pTa tumours and without CIS or dysplasia of the surrounding urothelium should have 2 or 3 check cystoscopies in the first year and annual checks thereafter. This would substantially reduce the number of cystoscopies which these patients have to undergo under most current follow-up protocols. As the risk of recurrence diminishes, flexible cystoscopy could be substituted for rigid cystoscopy, thus saving time and resources while remaining very acceptable to patients. The possibility of discharge after 5 years' disease-free follow-up has been raised by other workers. We have found that recurrence remains a small but significant risk after 5 years and so would not recommend discharge. Some have suggested follow-up with urine cytology alone after 5 years (England *et al.*, 1981) but cytology has a very low sensitivity for low grade tumours (Curling *et al.*, 1986) and is not an entirely satisfactory solution. A combination of urine cytology and extended flexible cystoscopy intervals may be an acceptable compromise for these low risk patients. Multiple pTa tumours have a higher risk of recurrence in the first and possibly second year after diagnosis and more frequent surveillance is necessary; however, we do not have sufficient numbers free from recurrence after 2 years to make firm recommendations on their long-term follow-up.

This study has shown that with adequate numbers of patients it is possible to estimate the annual risk of recurrence and then to use this to rationalise follow-up. The measurement of recurrence risks in bladder tumour patients should make a positive contribution to management by ensuring that the resources available for follow-up are targeted to those who would most benefit from them. We intend to extend this study to other groups of patients.

## Acknowledgements

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# Histopathological "Self Control" in Transurethral Resection of Bladder Tumours

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Summary—Between 1979 and 1989, 462 bladder tumours were resected in 319 patients using the differentiated technique. After transurethral resection (TUR) that was considered optically to be complete, histopathological examination of the specimen revealed residual tumour in 35% of cases. The danger of insufficient resection increases in relation to the depth of infiltration (pT) and is closely associated with the growth pattern of the tumour. The differentiated form of TUR is important in determining the depth of infiltration, peripheral expansion of the tumour and the completeness of removal.

Transurethral resection is essential in the diagnosis and treatment of patients with bladder tumours (Bressel *et al.*, 1969; Bichler *et al.*, 1982; Mauermayer, 1983). The procedure should include an assessment of tumour infiltration and centripetal extension, based on histopathological examination of samples removed at TUR.

## Patients and Methods

Since 1979, we have used a separate sampling method according to the system devised by Bressel (Kerenyi *et al.*, 1981; Csapo *et al.*, 1984).

We resect the tumour (sample 1) until no neoplastic tissue seems to remain. The surgeon then removes samples from the base of the crater remaining at the tumour site (sample 2) and from its lateral walls (samples 3–6). These 6 samples are sent separately for histopathological examination (Fig. 1).

Sample 1 allows assessment of the histopathological type, configuration and tumour grade. Samples 1 and 2 together reveal the depth of infiltration and samples 2 to 6 indicate whether the TUR was complete in terms of depth and extent. If the pathologist finds neoplastic tissue in any of samples 2 to 6, it indicates that the resection was inadequate and repeat TUR or even radical cystectomy may be required.

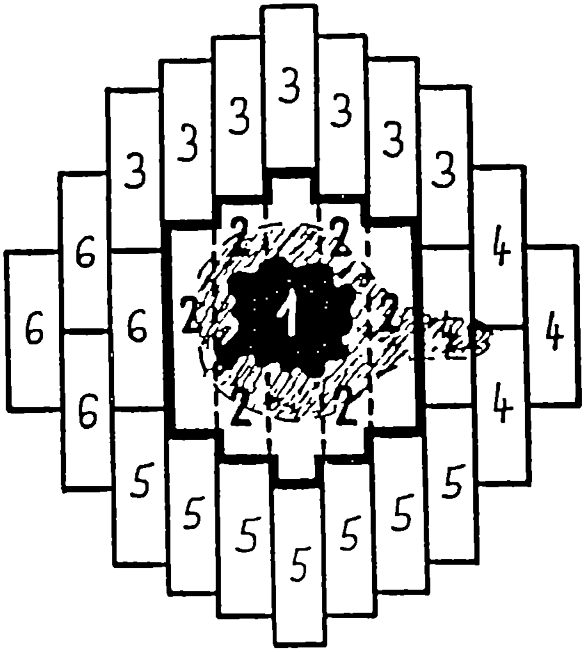

**Fig. 1** Differential transurethral bladder tumour resection according to Bressel *et al.* (1969). Sample 1: tumour mass. Sample 2: wound surface base apparently free of tumour. Sample 3: wound surface edge apparently free of tumour at 12 o'clock. Sample 4: 3 o'clock. Sample 5: 6 o'clock. Sample 6: 9 o'clock.

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**Table** Distribution of Tumours According to Stage and Grade

| | *G0* | *G1* | *G2* | *G3* | *Total* |
|---|---|---|---|---|---|
| TA | 88 | 130 | 46 | 3 | 267 |
| T1 | — | 25 | 26 | 7 | 58 |
| T2 | — | 3 | 19 | 12 | 34 |
| T3 | — | 4 | 19 | 69 | 92 |
| T4 | — | — | 3 | 8 | 11 |
| Total | 88 | 162 | 113 | 99 | 462 |

Between 1979 and 1989, 877 TURs were performed in this department and 462 tumours in 319 patients were resected according to Bressel's differentiating TUR technique. Histopathological examination revealed transitional cell papillary tumours in 344 cases (74.4%), solid (infiltrating) tumours in 76 (16.4%) and transitional cell tumours containing both papillary and solid components in 42 cases (9%). We found adenocarcinoma, which has an extremely poor prognosis, in 7 patients and squamous cell carcinoma in 3 patients, but these tumours were excluded from the present study. The Table shows the distribution of tumours according to stage and grade.

## Results

Residual tumour was identified in 163 cases (35%) following differential TUR. Sample 2 proved positive most frequently, *i.e.* tumour was left in the base in 120 cases in the course of the first TUR (Fig. 2). There was a relationship between residual neoplastic tissue and tumour configuration. In papillary tumours the residual tumour rate was 21.5% following the first TUR and 76% in the solid (infiltrating) or papillary/solid tumours. There was a close association between residual tumour and the depth of infiltration. Following the first TUR this amounted to 12.7% in pTa tumours, 36.2% in pT1 tumours, 55.9% in pT2 tumours and 83% in pT3 tumours. Perivesical adipose tissue was demonstrated in 76 cases by histopathological examination of sample 2.

## Discussion

Consistent use of an elaborate surgical procedure and the collection of separate samples is an essential part of TUR of bladder tumours (Kerenyi *et al.*, 1981; Bichler *et al.*, 1982). Histopathological examination of topographically classified and systematically processed tissue removed by TUR can establish the exact characteristics of tumours, such as configuration, histological type, grade of malignancy, depth of infiltration, centripetal tumour expansion and completeness of the endoscopic procedure.

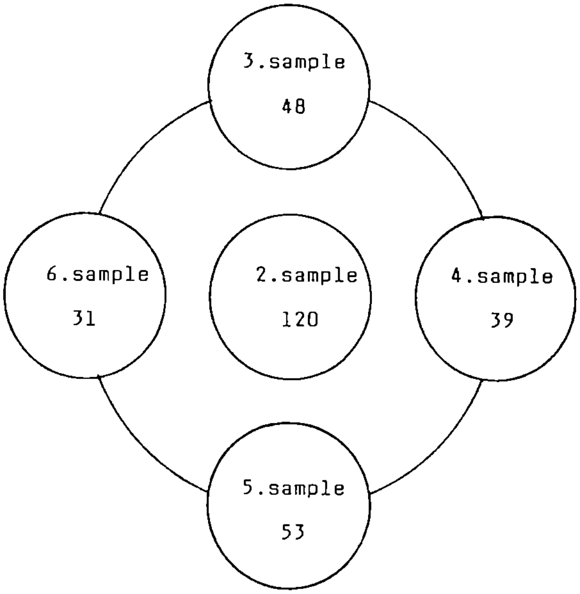

**Fig. 2** Numerical frequency and localisation of residual neoplastic tissue from TURs arranged in sequence according to Bressel's scheme.

Several authors deem it important to take tissue samples from the tumour base as well as from the grossly normal mucosa following TUR (Marberger *et al.*, 1972; Mauermayer, 1983). Bressel *et al.* reported their 6-point differential resection procedure in 1969 and Bichler *et al.* (1982) used it in 207 patients. The tumour was radically removed at the first TUR in 135 of these 207 patients and residual neoplastic tissue was found at histopathological examination in 72 cases; thus 2 or more resections were required. The frequency of neoplastic residuum increased commensurately with the depth of infiltration.

Our first and most important conclusion was the fact that neoplastic tissue would have remained in 35% of the tumours, *i.e.* every third patient regarded as tumour-free would have had residual tumour when discharged from hospital if we had not performed TUR by means of the differential resection technique (Fig. 2).

The 76% neoplastic residuum found in solid or papillary/solid tumours indicates the need for particular attention to be paid to these tumours during TUR.

If a tumour can be removed only by perforating the bladder wall, there is a significant risk of lymph node metastasis (Skinner, 1982) and in such cases radical cystectomy should be performed. If samples 2 to 6 contain no neoplastic tissue, the tumour can be regarded as radically removed (Kolozsy *et al.*, 1985).

The aim of this study was not to provide data on survival or the frequency of tumour recurrence in patients treated by TUR, but to present the immediate results obtained by using the differential resection technique.

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# Transferrin Receptor Activity as a Marker in Transitional Cell Carcinoma of the Bladder

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Summary—An immunohistochemical staining method was used to study transferrin receptors (TFR) in bladder tissue from 10 patients with benign conditions and 33 with bladder cancer. All patients with bladder cancer were followed up by cystoscopy at intervals of 3 months (mean follow-up period 11 months). The relationship between TFR activity and recurrence rates was investigated.

It was not possible to demonstrate TFR in normal bladder mucosa except for the proliferating cells of the basal layer. TFR activity in malignant tissue correlated well with the histological grade and pathological stage of the tumour. Patients with low grade superficial tumours showing TFR activity had a higher recurrence rate than those with no TFR activity.

It was concluded that TFR activity in low grade superficial bladder tumours is a useful marker for predicting the recurrence rate.

Bladder cancer has 2 modes of biological behaviour, invasive and non-invasive. At presentation, it is important to assign patients to the appropriate group because those in the former group require intensive radical treatment while those in the latter can be managed conservatively. Many clinical, laboratory and pathological investigations are used to differentiate between the 2 groups (Javadpour, 1984).

In some cases, conventional prognostic factors fail to predict the potential aggressiveness of the tumour. This is especially true for some superficial low grade tumours which are managed by endoscopic resection, with or without intravesical chemoprophylaxis, and which recur frequently. In order to predict the natural history and biological behaviour of bladder cancer a reliable marker is still needed (Seymour *et al.*, 1987).

Transferrin and its receptor are essential in making iron available for cellular use (Bomford and Munro, 1985). Transferrin receptor is a cell surface protein found in high numbers in rapidly proliferating benign and malignant tissues and also in those cells that use iron for specific purposes, *e.g.* haemoglobin-producing cells and placental trophoblasts. In many studies, TFR has been shown to increase in malignant tissue and this includes bladder tumours (Faulk *et al.*, 1980; Gatter *et al.*, 1983; Lloyd *et al.*, 1984).

The purpose of this study was to demonstrate TFR in benign and malignant bladder tissue and to investigate the relationship between TFR activity and the grade and stage of the original tumour. The relationship between TFR activity and recurrence rate was also investigated.

## Patients and Methods

The study group included 33 patients who underwent complete removal of bladder tumour by transurethral resection (TUR) and 10 patients who underwent cystoscopy for benign conditions. The tumour group consisted of 28 males and 5 females (mean age 68.8 years, range 44–80). The control group comprised 8 males and 2 females (mean age 58.2 years, range 42–76).

Pre-operative investigations included haemo-

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graphy, urine analysis, chest X-ray, intravenous urography and abdominal ultrasonography. A pelvic CT scan was also performed on some occasions. Before TUR, each patient was evaluated by bimanual examination under general anaesthesia.

Tissue specimens obtained either by TUR or by punch biopsy forceps were subdivided. One portion was immediately transported in liquid nitrogen to a freezer where all tissue was stored at −70°C until used. The other portion was sent for routine histopathological examination.

To demonstrate TFR in tissues, the avidin-biotin immunoperoxidase staining method was used (Taylor, 1978). From the tissues 7-micron frozen sections were cut, air-dried and fixed for 5 min in acetone. The sections were then transferred to a phosphate buffered saline solution (PBS) and rehydrated for 10 min. The primary antibody, monoclonal mouse anti-human transferrin receptor antibody (Dako-Tf-R, Dakopatts, Catalogue No. M734) at a dilution of 1:30 in PBS was then applied for 30 min. The sections were incubated with sheep anti-mouse immunoglobulin (Dakopatts, Catalogue No. E354) at 1:400 affinity for 30 min. At the third stage, the sections were incubated with 1:500 affinity streptavidin horseradish peroxidase (Dakopatts, Catalogue No. K377). After each incubation the slides were washed in PBS. At the final stage, peroxidase substrate solution (0.06% diaminobenzidine and 0.3% hydrogen peroxide) was applied for 10 min. The sections were washed in distilled water and counterstained by haematoxylin. From each specimen a frozen section was also stained directly by haematoxylin and eosin and examined to confirm the diagnosis of tumour. Some sections were stained without using the primary antibody in order to confirm that the immunostaining was not non-specific. Endogenous peroxidase is not present in significant amounts in the cells of bladder epithelium and therefore did not have to be blocked.

The histopathological grade and stage of the tumours were determined by examining the haematoxylin and eosin stained sections prepared from the paraffin blocks. The histological composition of each tumour was categorised according to the classification of the World Health Organisation (Mostofi *et al.*, 1973). For pathological staging the TNM (1978) staging system was used (Chisholm *et al.*, 1980).

All patients with bladder tumours were followed up by cystoscopy at intervals of 3 months.

Fisher's exact $\chi^2$ test was used for statistical analysis.

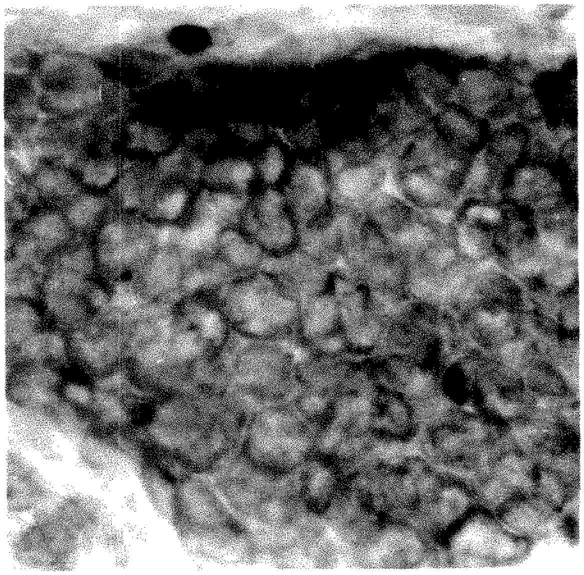

**Fig.** TFR-positive staining in high grade tumour tissue. (Strept-ABC immunoperoxidase, anti-TFR ×460).

## Results

TFR activity was characterised by a brown-coloured line of demarcation at the cell surface and/or by a less intense brown-coloured diffuse cytoplasmic staining (Fig.). In some sections there was no such staining except for the macrophages, reticulocytes and muscle cells. Sections with no staining at all or with only weak cytoplasmic staining were accepted as TFR-negative tumours, while those with the brown-coloured demarcating line at the cell border were accepted as TFR-positive tumours.

There was no TFR-positive staining in any of the biopsies from control patients except for the proliferating cells of the basal layer.

Six of 15 patients (40%) with grade I/III tumours were TFR-positive, while 17 of 18 grade II–III/III tumours (94%) were TFR-positive; 30% of pTa tumours (confined to the mucosa), 73% of pT1 tumours (invading lamina propria only) and 100% of pT2+ tumours (invading muscle and beyond) were TFR-positive.

Of 18 high grade tumours (Grade II–III/III), 17 were TFR-positive; 13 of these patients were eliminated from the study (1 post-operative death, 2 underwent radical surgery and 10 received intravesical therapy). The remaining 5 patients were followed up by cystoscopy and all had recurrences.

A total of 15 patients with grade I/III and stage pTa–pT1 tumours were followed up cystoscopically without any form of intravesical therapy. After a mean follow-up of approximately 11 months the recurrence rate was 100% for TFR-positive and 44% for TFR-negative tumours. The total number of recurrences in this group was 8 in the TFR-positive and 5 in the TFR-negative tumours. None of these 13 recurrences was accompanied by progression in grade or stage.

## Discussion

Grade and stage, as determined by conventional histopathological means, do not always provide information on the biological behaviour of bladder cancer. Over the last 10 years, considerable efforts have been made to find more reliable markers, including determination of cell surface antigens, chromosomal analysis, flow cytometry and cytology (Javadpour, 1984).

More recently, the expression of growth factors and oncogene products have improved the detection of high and low risk bladder cancer (Neal *et al.*, 1985; Viola *et al.*, 1985). It was suggested that sequential activation of oncogenes, growth factors and growth factor receptors results in the expression of TFR by the cells (Neckers and Trepel, 1986). In the study by Wiley and Kaplan (1984) it was found that epidermal growth factor increased the number of TFRs on the cell surface and caused cell growth by redistributing TFR pools in human fibroblasts. Neckers and Trepel (1986) found that despite strongly induced growth factor receptors and elevated oncogene levels, lymphocyte proliferation was blocked if TFR induction was inhibited. Thus the increase in TFR activity is probably the last stage in events which determine the proliferative activity of tumour cells. Expression of TFR can be considered a more functional marker than oncogene products and growth factors for determining the biological behaviour of the tumours.

In the present study, malignant tissue from some bladder cancer patients and normal tissue from control patients showed no TFR activity. The presence of TFR activity in proliferating normal epithelium and in some tumour tissue indicates the possibility that bladder epithelium has a latent ability for synthesising TFR.

There was an excellent correlation between TFR positivity and the grade and stage of the tumour. This finding was similar to that noted in the study by Seymour *et al.* (1987). In our study it was not possible to evaluate these prognostic factors independently because most of the high grade tumours were also invasive and most of the low grade tumours were superficial.

In patients with low grade, pTa–pT1, TFR-positive tumours the recurrence rate was significantly higher than in patients with TFR-negative tumours in the same group. The distribution of grade and stage in these tumours was comparable, suggesting that TFR expression is the sole factor influencing the recurrence rate in this group.

The tumour sections showed varying intensities of staining. In fact, the presence of TFR on cells is not related to an "all-or-none" principle and it is not always easy to describe a cut-off point for TFR positivity. In a number of studies investigating the cell surface receptors, certain criteria have been described for determining receptor positivity (Neal *et al.*, 1985; Seymour *et al.*, 1987).

The avidin-biotin immunoperoxidase staining method is an expensive and time-consuming procedure. For this reason, the use of TFR expression as a routine procedure for bladder tumours is justifiable only if its predictive value in determining the prognosis is greater than the information supplied by conventional prognostic factors. We conclude that TFR activity can be a useful marker for predicting the recurrence rate of low grade, pTa–pT1 tumours and feel there is sufficient evidence to recommend this method as part of the routine investigation of patients with bladder cancer at presentation.

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# Systemic Chemotherapy for Urothelial Cancer in Patients with Ureteric Obstruction

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Summary—The aims of this study were to document the toxicity of systemic chemotherapy and response rates in patients with ureteric obstruction caused by urothelial cancer.

The study group included 91 patients who received cisplatin and methotrexate; 36 (40%) had upper tract dilatation, 9 of whom had drainage by stenting or nephrostomy and 55 (60%) had normal upper tracts. The response rate was documented in 65 patients (71%) who had measurable primary or metastatic disease.

No significant differences were found between the dilated/drained group, the dilated/undrained group and the normal group in biochemical measurements of renal function during or after the courses of chemotherapy. Serious haematological toxicity occurred in 10% (10/104 cycles) of the dilated/undrained group and in 6% (12/200 cycles) of the normal group. The complete response rate in the dilated group was 15% compared with 41% in the normal group.

No increased chemotherapy toxicity was observed in patients with upper tract dilatation and a significant complete response rate was found in patients with upper tract dilatation without renal impairment.

The last 5 years have seen the introduction of chemotherapy for invasive transitional cell carcinoma (TCC) of the urinary tract following encouraging reports of single agents such as doxorubicin (Yagoda *et al.* 1977), methotrexate (Turner *et al.*, 1977) and cisplatin (Fagg *et al*, 1984; Raghavan *et al.*, 1985). Recent results with chemotherapy include a complete response rate of about 24% in the primary tumour after neoadjuvant chemotherapy for invasive bladder cancer (Carmichael *et al.*, 1985; Scher *et al.*, 1988; Roberts *et al.*, unpublished data). In addition, more than half of the complete responders with metastatic disease were alive at 26 months (Sternberg *et al.*, 1988).

Ureteric obstruction caused by invasive bladder cancer has a poor prognosis, with 5-year survival rates ranging from 5 to 28% (Greiner *et al.*, 1977; Batata *et al.*, 1981; Mameghan *et al.*, 1989). Most combination chemotherapy regimes use cisplatin and methotrexate, but the toxicity of both is increased if renal function is impaired. Many invasive bladder tumours cause ureteric obstruction and, because of their poor prognosis, such patients have potentially the most to gain from innovative treatments.

We have reviewed our chemotherapy results to determine if there was any increase in toxicity and if response rates warranted the continued use of chemotherapy in patients with ureteric obstruction.

## Patients and Methods

Over the past 3 years, 102 patients have been treated with systemic chemotherapy for invasive TCC; 91 had adequate documentation of the state of the upper urinary tracts and response to treatment (Table 1). The median age was 65 years (range 34–83).

Ten patients had T2 tumours, 43 had T3 tumours and 14 had T4 tumours without metastases (UICC, 1974); 20 patients had measurable metastases as the indication for starting chemotherapy and 4

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**Table 1** T Stage and State of Upper Tracts at Start of Chemotherapy

| *Tumour* | *Upper tracts* *Normal* | *Dilated* | *Total* |
|---|---|---|---|
| T2 | 9 | 1 | 10 |
| T3$\leq$5 cm | 18 | 8 | 26 |
| T3$>$5 cm | 8 | 9 | 17 |
| T4 | 7 | 7 | 14 |
| TXNXM1 | 9 | 11 | 20 |
| Extravesical tumour | 4 | 0 | 4 |
| Total | 55 | 36 | 91 |

additional patients underwent chemotherapy following excision of bulky primary upper tract TCC. No patient had prior radiotherapy.

Of the 91 patients, 55 had normal upper tracts (60%) and 36 had upper tract dilatation (40%) on IVU or CT scan. This was unilateral in 22 patients and drained by endoscopic stent or nephrostomy in 5. It was bilateral or involved a solitary kidney in 14 patients and 4 of these patients were drained, 2 because the serum creatinine exceeded 200 μmol/l and 2 owing to fear of potential toxicity from the chemotherapy.

Patients were given 1 of 4 types of systemic chemotherapy, with cisplatin (70mg/m$^2$) and methotrexate (30–40 mg/m$^2$) according to the following protocols; M-VAC (Sternberg *et al.*, 1985); MRC phase II study of cis-platinum and methotrexate in T3/4 bladder cancer; EpiC-M: a 3-week cycle of Day 1-epirubicin 50 mg/m$^2$ and cisplatin 70 mg/m$^2$ and Days 8 and 15-methotrexate 40 mg/m$^2$ as a bolus; and EORTC protocol number 30851. Each protocol included pre- and post-hydration around the cisplatin infusion and frequent checks of blood count and serum creatinine.

The 46 patients who had neoadjuvant chemotherapy for primary carcinoma of the bladder were followed up by means of cystoscopy with deep resection biopsies at the site of their former tumour after 2 cycles of treatment. If the tumour showed a partial or complete response after 2 cycles, the patient proceeded to a further 2 cycles. Most patients with complete responses received a total of 6 cycles. If the tumour failed to respond after 2 cycles or if there was only a partial response after 4 cycles, another treatment modality was instituted. The response to chemotherapy for metastatic disease was measured after each 2 or 3 cycles by CT or ultrasound scan.

The glomerular filtration rate (GFR) was estimated either by EDTA clearance (n=76), 24-h creatinine clearance (n=4) or by estimation using serum creatinine and body weight (n=11). The dose of cisplatin was reduced in patients with GFR$<$60 ml/min.

Renal function was monitored in all cases by serial serum creatinine estimations. For the purpose of analysis, serum creatinine was recorded on day 1 of cycle 1, and the day of the last injection of methotrexate, during the fourth or last cycle. This method was adopted to reduce bias between non-responders and responders, because the latter had more cycles of chemotherapy.

The second measure of renal toxicity was the development of renal impairment, which was defined as a rise in serum creatinine of more than 30% plus a final value of more than 120 μmol/l.

Bone marrow toxicity was assessed by the WHO (1979) classification as well as the incidence of nadir sepsis (severe sepsis at the time of a depleted white cell count).

The response rate is reported only in the 65 patients who received neoadjuvant chemotherapy for measurable disease (Raghavan, 1988). A complete response was defined as the absence of any tumour on resection biopsy at the site of the former tumour. A partial response was a $\geq$50% reduction in the size of the tumour measured as the product of 2 maximum diameters assessed by examination under anaesthesia, CT scan or both.

Differences were tested by applying the Mann-Whitney U test, taking $P<0.05$ on a 2-tailed table of distribution as significant, or the $\chi^2$ test with Yates' correction and taking $P<0.05$ as significant.

Ethical committee approval was granted for each of the trials of chemotherapy protocols.

## Results

The stage of disease at the start of chemotherapy is shown in Table 1; patients with upper tract dilatation started chemotherapy with significantly higher stage disease than the patients with normal upper tracts. Of the patients with localised disease, the primary was T2 or small T3 ($<$5 cm) in 36% of patients with upper tract dilatation, but in 64% of those with normal upper tracts (Table 2, $\chi^2=11.3$, for 1 DF $P<0.05$). The patients were further classified according to the state of the upper urinary tract, *i.e.* normal, dilated/drained or dilated/undrained.

No significant differences in median creatinine, change in creatinine or the development of renal impairment were found among any of the 3 groups (Tables 2 and 3). Similarly, there was no significant

**Table 2** Renal toxicity

| | *Serum creatinine (μmol/l)* | |
|---|---|---|
| | *Before chemotherapy Median (range)* | *After chemotherapy Median (range)* |
| Normal (n = 55) | 96 (66–135) | 112 (73–246) |
| Dilated/drained (n = 9) | 117 (106–503) | 127 (83–147) |
| Dilated/undrained (n = 27) | 116 (78–218) | 123 (80–253) |

Before chemotherapy 35% of patients had a creatinine >120 μmol/l.

**Table 3** Incidence of Impaired Renal Function at the End of Chemotherapy

| *Upper tracts* | *No.* | *(%)* |
|---|---|---|
| Normal | 13/55 | (24) |
| Dilated/drained | 1/9 | (11) |
| Dilated/undrained | 6/37 | (22) |

difference in the GFR measured by EDTA clearance in patients with upper tract dilatation (n = 31; median = 70 ml/min; 1st and 3rd quartiles = 55 and 83) compared with patients whose upper tracts were normal (n = 45; median = 86 ml/min; 1st and 3rd quartiles = 72 and 103). However, significantly more patients with upper tract dilatation had a GFR <60 ml/min compared with those with normal upper tracts (11/31 *vs* 5/45, $\chi^2 = 6.6$, $P = 0.01$). Hence a reduced dose of chemotherapy was used more frequently in the group with upper tract dilatation.

Three patients developed clinically significant renal failure. The first developed acute renal failure when given frusemide after the cisplatin infusion of his second cycle and he required a short period of dialysis before spontaneous recovery. The second patient developed acute renal failure complicating malignant hypercalcaemia and died with rapidly progressing disease. The third developed acute obstructive renal failure immediately following a check cystoscopy 3 months after finishing chemotherapy and 6 weeks after finishing radiotherapy. This patient also died.

Episodes of haematological toxicity (Table 4) were found slightly more frequently in the dilated/undrained group, but this was not statistically significant compared with the other groups.

There were 5 deaths within 3 months of chemotherapy, in addition to the 2 mentioned above: 1 was due to a perforated peptic ulcer and the others to advancing malignancy. Of the 7 deaths, 3 occurred in patients with normal upper tracts.

**Table 4** Episodes of WHO Grade 3/4 Marrow Toxicity/Cycles Given

| | *No.* | *(%)* |
|---|---|---|
| Normal | 12/200 | (6) |
| Dilated/drained | 1/25 | (4) |
| Dilated/undrained | 9/79 | (11) |

**Table 5** Complete Response to Neoadjuvant Chemotherapy

| | *Upper tracts* | |
|---|---|---|
| *Tumour stage* | *Normal* | *Dilated* |
| T2–4 | 12/23 | 4/22 |
| M > 0 | 1/9 | 1/11 |
| Total | 13/32 | 5/33 |

In the 65 patients with measurable primary or metastatic lesions, there were significantly fewer complete responses in the patients with upper tract dilatation (5/33; 15%) compared with the patients with normal upper tracts (13/32; 41%; $\chi^2 = 4.1$; $P < 0.05$) (Table 5). There were also significantly more complete responses in the bladder primaries of the patients with normal upper tracts and bladder tumours (12/23; 52%) compared with the group with dilated upper tracts (4/22; 18%, $\chi^2 = 4.3$; $P < 0.05$). There was 1 complete and 2 partial responses among the 10 patients with bilateral dilated and undrained upper tracts.

It should be noted that of the 3 patients who had a creatinine exceeding 200 μmol/l at presentation, only 1 achieved a partial response and the other 2 progressed. There were a further 18 patients with a creatinine of 120 to 200 μmol/l at the start of their chemotherapy; 6 of these had normal and 12 had dilated upper tracts. There were 3 complete responses in the normal group and 1 in the dilated group.

Thus only 1 complete response was found in 15 patients with creatinine > 120 μmol/l and dilatation of the upper tracts (7%).

## Discussion

The role of systemic chemotherapy in the treatment of muscle invasive bladder cancer is presently being explored. The data from this study suggest that it can be given safely to patients with bladder cancer, many of whom are elderly with compromised cardiovascular systems and renal impairment, even to those with upper tract dilatation.

Serial measurement of serum creatinine was used to monitor renal function during chemotherapy and in the definition of the development of renal impairment. This approach is known to be useful for following up changes in renal function in individual patients (Morgan and Will, 1983), though isolated measurements of serum creatinine do not correlate well with GFR. As a result of this, the planning of chemotherapy doses was based on the measurement of GFR.

Based on previous reports (Barton *et al.*, 1988), we might have expected increased renal toxicity in patients with upper tract dilatation and a normal GFR and there is no obvious explanation of why this did not occur. However, we also found little improvement in renal function in patients with upper tract dilatation, which might have happened had the primary tumours responded well.

We also expected increased bone marrow toxicity in patients with upper tract dilatation. This was indeed manifest until the introduction of routine folinic acid rescue. We would recommend routine folinic acid rescue when methotrexate is used in patients with impaired renal function or upper tract dilatation.

Complete responses were found in patients with upper tract dilatation, but in a lower proportion than in those with normal upper tracts. Moreover, in patients with a combination of upper tract dilatation and impaired renal function only 1 patient achieved a complete response, which may question the role of such treatment in patients with renal impairment caused by advanced bladder cancer. There are 2 possible causes of this lower response rate. The first is that the patients with upper tract dilatation presented with significantly higher stage disease and the second is that significantly more of these patients were given reduced doses of chemotherapy because of their low GFR. This study was unable to establish which of these causes accounted for the differences seen.

Our data suggest that systemic chemotherapy which includes cisplatin can produce significant response rates in patients with upper tract dilatation who have normal renal function, but the response rate was low in patients with advanced local disease, upper tract dilatation and renal impairment.

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# Diagnosis of Chronic Abacterial Prostato-vesiculitis by Rectal Ultrasonography in Relation to Symptoms and Findings

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Summary—A group of 36 men with chronic abacterial prostato-vesiculitis, confirmed by semen analysis and rectal ultrasonography, underwent detailed anamnesis and clinical examination. There was no clear relationship between the severity of the symptoms or the presence of leucocytes and the extent of the changes visualised by ultrasound. In 72% of cases, clinical examination also revealed signs of a previous epididymitis. In general, asymmetry in symptoms could be related to glandular pathology, as indicated by ultrasonography, on the ipsilateral side.

Until recently, chronic abacterial prostato-vesiculitis was largely an exclusions diagnosis, based on clinical suspicion of an inflammatory condition in the sex glands without the classical finding of significant numbers of pathological bacteria in the seminal plasma. In recent years, rectal ultrasonography has become a valuable diagnostic aid in screening for prostatic cancer (Lardennois and Brandt, 1985; Waterhouse and Resnick, 1989). A natural extension was the use of ultrasound to demonstrate other pathological conditions in the accessory sex glands, not only in the prostate but also in the seminal vesicles. We have used this technique to study and confirm the presence of chronic abacterial prostato-vesiculitis. The present report describes the symptoms and findings in 36 men where this condition was verified by rectal ultrasonography.

## Patients and Methods

The study group comprised 36 men aged from 19 to 49 years (median 35); 31 were referred because of a long history of symptoms in the lower abdomen and/or perineum. An additional 5 were symptom-free and were examined as part of an infertility investigation. Detailed anamnestic information was collected with emphasis on previous and present symptoms. There followed a detailed clinical examination of the scrotal contents, particularly of the epididymis, and rectal palpation of the accessory sex glands. All examinations were carried out by the same person (E.C.).

Semen analyses were carried out on all patients as described previously (Purvis *et al.*, 1989a, b) after an abstinence period of 3 to 5 days and a liquefaction period of 20 min. In all cases the concentration of leucocytes was determined according to Purvis *et al.* (1989b). Aliquots of the ejaculates were also sent for bacterial culture under anaerobic and aerobic conditions. In a number of patients, urine and samples of prostatic fluid were obtained using Stamey's 4-glass method (Meares and Stamey, 1968) and these were also sent for bacterial culture. No difference was found in the results of bacterial culture using both methods. Furthermore, since semen obtained after ejaculation is the result of a more physiological and representative emptying of the sex glands, subsequent cultures were performed on liquified ejaculates.

All patients were examined by rectal ultrasonography (Brüel and Kjær no. 1849, rectal probe no. 1850) with a transverse scanning transducer (no. 8539, 7 MHz) by the same physician. Photographic records of the ultrasound images of both the prostate gland and the seminal vesicles were included in the case records for later comparison. In the case of the prostate gland, emphasis was placed on asymmetrical changes in the peripheral zone since, in our experience, this is the area usually affected in cases of chronic inflammation. In addition, the presence of concrements and/or cysts or abscesses was noted,

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especially in the outer capsule, which was often thickened. Alterations in echogenicity within the substance of the gland which indicated areas of oedema were also recorded (Figs 1 and 2). In the case of the seminal vesicles, large variations in form and size both within and between patients were apparent. In accordance with guidelines published elsewhere (Di Trapani *et al.*, 1988; Littrup and Lee, 1988), the following were taken as indicative of chronic inflammation: elongation of the seminal vesicles, major thickening of the walls of the gland, signs of fluid retention and the presence of internal septa (Figs 3 and 4). It was often possible to see one or both of the vesicles as club-shaped structures extending down to the back of the rectum. Under such conditions the rectal probe is well suited for visualising the extent of these morphological changes because of its ability to decentralise the image and scan the entire rectal circumference.

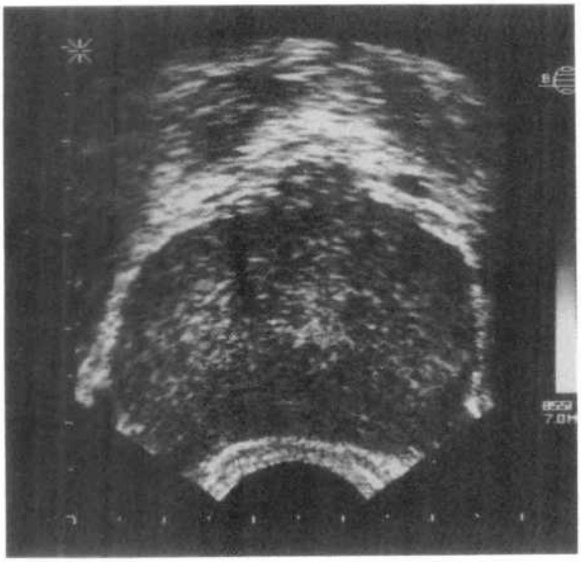

**Fig. 1** Transverse scan of normal prostate.

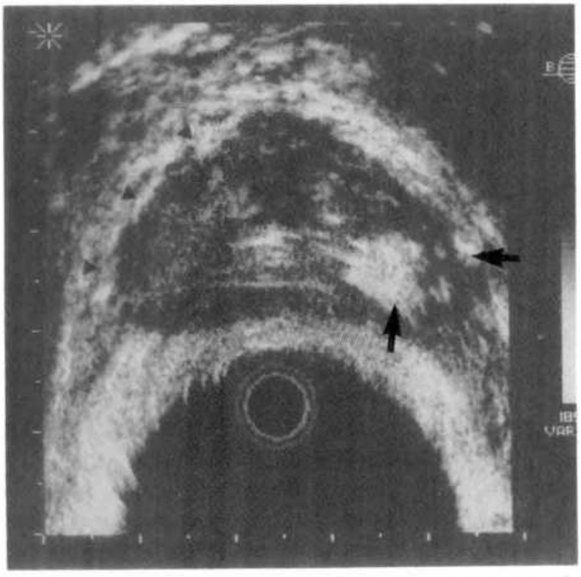

**Fig. 2** Prostatitis. Thickened capsule (small arrows) and calculous mass with associated oedema (large arrows).

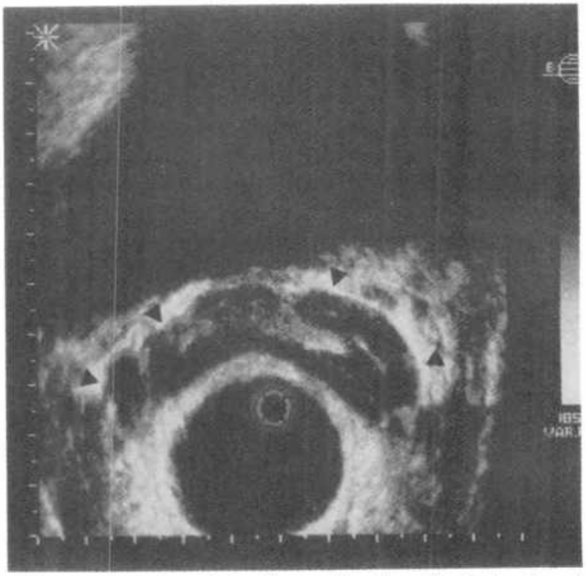

**Fig. 3** Vesiculitis with significant dilatation of both glands and thickening of internal septa.

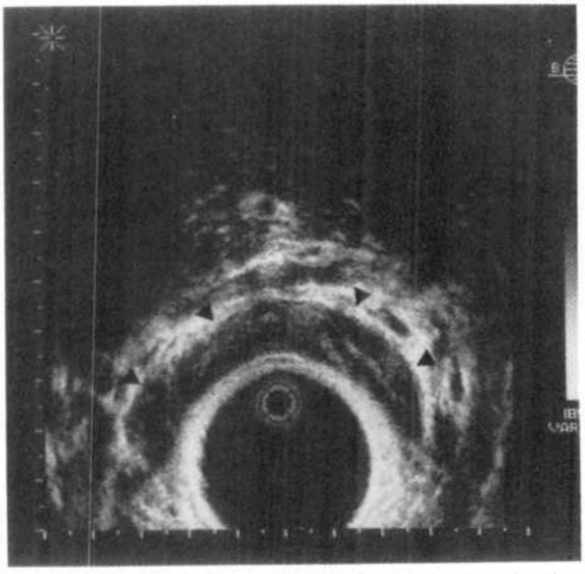

**Fig. 4** Same patient as in Figure 3, after ejaculation, showing reduction in the diameter of the glands but with more conspicuous internal septa.

## Results

The Table summarises the nature and frequency of symptoms in the 36 men with chronic abacterial prostato-vesiculitis verified by rectal ultrasonography. There was great variation in the symptoms reported, although the most frequent site of discomfort or pain was the perineum or scrotum, often in connection with ejaculation. Frequency of micturition, dysuria and reduced urine flow were also relatively common associated symptoms. The following 4 case reports illustrate the variable nature of the symptoms and the resulting diagnostic problems associated with this condition.

*Case 1.* A 23-year-old man was referred with chronic pain in the left inguinal area and perineum and large clumps in the ejaculate. His social life was affected by the pain and discomfort, which he admitted could only be relieved by frequent masturbation. Clinical examination indicated extreme discomfort over both capita epididymides and rectal exploration revealed a left prostatic lobe which was extremely painful on palpation. Bacterial culture of the seminal plasma indicated the presence of *Escherichia coli* but not in significant numbers. Rectal ultrasonography recorded changes suggestive of chronic prostato-vesiculitis with involvement of both vesicles.

*Case 2.* A 33-year-old man had experienced pain with ejaculation over a 4-year period. The pain and discomfort, which increased during the excitement phase and reached a maximum at ejaculation, emanated from the perineum and penis and radiated along the urethra. Three years earlier the patient had been successfully treated for a chlamydial infection. On examination he was depressed and had voluntarily abstained from all sexual activity over a long period. The prostate was extremely tender and boggy. In the scrotum the right caput epididymis was very firm and painful. The ejaculate contained a few leucocytes and bacterial culture was negative. Ultrasonography revealed numerous concrements in the central region of the prostate, peripheral areas of oedema and a thick-walled abscess under the capsule on the right side. The seminal vesicles had a normal appearance.

**Table** Nature and Frequency of Symptoms Associated with Chronic Abacterial Prostato-vesiculitis

| *Symptom* | *Incidence* |
|---|---|
| Discomfort/pain in perineum | 20 |
| Discomfort/pain in scrotum | 15 |
| Discomfort/pain with ejaculation | 12 |
| Frequency of micturition | 11 |
| Dysuria | 9 |
| Reduced urine flow | 7 |
| Discomfort/pain over symphysis | 7 |
| Urgency | 5 |
| Discomfort/pain inner aspect of thigh(s) | 4 |
| Discomfort/pain in penis | 3 |
| Haematospermia | 3 |
| Low back pain | 3 |
| Clumps in the ejaculate | 2 |
| Haematuria | 2 |
| Nocturia | 2 |
| After drip | 2 |
| Asthenia | 2 |
| Discharge | 1 |
| Joint pain | 1 |
| Reduced potency | 1 |
| Asymptomatic* | 5 |

*After routine fertility examination.

*Case 3.* In 1975 a 43-year-old man had an episode of pain in the lower abdomen radiating to both inguinal areas which was interpreted as acute prostatitis. After antibiotic treatment the symptoms disappeared. Over the last 2 years he gradually developed similar symptoms with pain localised to both groins and scrotum. Short-term courses of antibiotics failed to alleviate his symptoms. Surgical exploration of both inguinal areas to exclude the possibility of hernia yielded negative results. Examination at our clinic revealed extreme discomfort with palpation of the cauda epididymis on the left side. The prostate was normal on rectal palpation but rectal ultrasonography showed marked oedema localised to the left prostatic lobe and enlargement of both seminal vesicles. There was no evidence of pathogenic bacteria in the seminal fluid.

*Case 4.* A 40-year-old man had a 20-year history of dysuria after ejaculation and reduced urine flow. His partner had recurrent non-specific vaginitis, especially after coitus. He had microhaematuria but culture of both urine and semen revealed only non-specific urethral flora. There were no positive findings with cystoscopy, urography and abdominal CT. Glomerulonephritis was suggested as a tentative diagnosis. Rectal ultrasonography indicated a prostate of normal size but with marked prostatitis changes in the right prostatic lobe and gross enlargement of the seminal vesicle on the left side.

In these and other patients, there was no clear association between the intensity of the symptoms reported and the degree of pathological changes indicated by ultrasonography. In 5 men who were examined as part of a routine infertility investigation and who were symptom-free, clear sonographic evidence was obtained of major inflammatory changes in both the prostate and the seminal vesicles. The number of leucocytes in the ejaculate did not predict the presence or degree of glandular pathology indicated by ultrasound. Of those examined, only 48% exhibited leucospermia with a leucocyte concentration exceeding 1 million/ml. In 68% of patients, inflammatory changes were observed in the prostate gland and seminal vesicles.

Moreover, in many cases (72%), clinical examination revealed past or present involvement of the epididymides, with cysts or a thickened, painful epididymis in the transitional zone from caput to corpus.

In the majority of cases, symptoms were asymmetrical and showed no preference for a particular side. In all of these patients, rectal ultrasonography confirmed that the glandular changes were more manifest on the side where the symptoms were focused. In cases of asymmetric inflammation, clinical investigation invariably revealed evidence of epididymitis on the ipsilateral side.

## Discussion

The present study indicates the diversity of symptoms associated with chronic abacterial prostato-vesiculitis and emphasises the use of rectal ultrasonography as an aid in diagnosing the condition. Marked inflammatory changes can occur in the sex glands without obvious symptoms, as indicated in the 5 infertile men. There were sufficient grounds to believe that these asymptomatic men had experienced previous episodes of mild, transitory discomfort but had not sought medical advice. Such cases emphasise the dilemma in diagnosing chronic inflammatory conditions of the sex glands. Bacterial culture of the ejaculate is invariably disappointing, no emphasis can be placed on the concentration of leucocytes in the secretory fluids, and clinical examination is limited because of the relative inaccessibility of the seminal vesicles.

Under such conditions, it is an important preventive measure to follow up (using ultrasonography) those young men who have reported any symptoms, no matter how minor, from the scrotum or perineum. The consequences of overlooking these episodes may be irreversible epididymal obstruction and sterility. An important consideration in this respect is that in a large number of patients there was a triad of prostato-vesiculo-epididymal involvement, implying that in patients with newly discovered prostatitis there may be a considerable risk of the inflammatory process spreading to other parts of the reproductive system. This is further indicated by the asymmetry of the symptoms and the pathological changes: a right-sided prostatitis is often associated with involvement of the seminal vesicle and epididymis on the same side.

Pain or discomfort in the perineum appeared to be associated with a distended seminal vesicle. Major distension of these glands was associated with radiation of pain to the scrotum or inner aspect of the ipsilateral thigh. This discomfort or pain could be reproduced by a 5-ml bolus injection of a mixture of antibiotic and local anaesthetic into one of the vesicles, transperineally and guided by ultrasound (unpublished observations). The implications are that this type of discomfort, associated with vesiculitis, is caused by referred pain from the gland under tension as a result of retained secretion. In some cases this referred pain may mask an epididymal involvement.

The increasing interest in the application of ultrasound to the diagnosis of inflammatory conditions in the male accessory sex glands will probably reveal the condition to be far more widespread than was previously suspected, based on conventional criteria and clinical examination. The involvement of glandular pathology in the aetiology of male infertility emphasises the need to include rectal sonography in routine investigation of male fertility.

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# Dilatation of the Prostatic Urethra with 35 mm Balloon

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Summary—A series of 54 men, 25 with acute urinary retention and 29 with cystometrically proven bladder outflow obstruction (BOO), underwent dilatation of the prostatic urethra using a 35 mm fixed diameter, low compliance balloon. In 42 patients this was performed under cystoscopic guidance and in 12 patients under fluoroscopic control.

Three months following dilatation, 13/27 patients (48%) with BOO who returned for review were rendered unobstructed and 19/27 (70%) were symptomatically improved. By 6 months only 3 remained unobstructed but 15 remained symptomatically improved. Nine months after dilatation 14 patients retained symptomatic improvement but only 2 remained unobstructed. Of the 25 patients treated for acute retention only 6 voided spontaneously, 1 of these relapsing into retention at 2 months and another at 4 months. No patient was rendered unobstructed but 2 patients (who declined prostatectomy) noted an improvement in their obstructive symptoms at both 3 and 6 months. No patient developed retrograde ejaculation following dilatation.

Balloon dilatation to 35 mm has no role in acute urinary retention but may have a role in younger men with BOO who wish to avoid prostatectomy and the risk of retrograde ejaculation. In these patients careful follow-up is required.

Several workers have advocated the use of balloon dilatation of the prostate in the management of bladder outflow obstruction (Castaneda *et al.*, 1987, 1988; Reddy *et al.*, 1988). In the majority of studies the results have been based on symptomatic or flow rate analysis (Castaneda *et al.*, 1987; Reddy *et al.*, 1988; Klein and Lemming, 1989). Gill *et al.* (1989) observed that cystometric assessment of patients dilated to 20 and 25 mm showed that only 11% were rendered unobstructed despite almost 50% obtaining symptomatic relief.

Castaneda *et al.* (1988) postulated that the effect of balloon dilatation was primarily related to its ability to produce a successful commissurorotomy. To date, investigators have used balloons of 8, 10, 15, 20 and 25 mm diameter. Klein and Lemming (1989) observed that as balloon diameter increased, so did the diameter of the prostatic urethra, and thus a commissurotomy became more likely. On this basis we evaluated a purpose-built balloon which, when inflated, attained a diameter of 35 mm (105 F). To our knowledge, this is the first description of the use of such a large diameter balloon in the treatment of patients with BOO and acute retention.

## Patients and Methods

All patients underwent symptomatic assessment using a standardised questionnaire and physical examination. Prostatic size was estimated by a single observer by digital palpation *per rectum*. Patients with symptoms of bladder outflow obstruction underwent free flow rate estimation followed by inflow and voiding cystometry. Patients whose urethral resistance exceeded 0.5 cm.$H_2O/s^2/ml^{-2}$ (Coolsaet and Blok, 1986) were considered obstructed and were offered dilatation. Patients catheterised for acute retention underwent cystometry alone, following initial symptomatic and physical assessment, and all were offered dilatation. Informed consent was obtained from all patients. Dilatation was performed on an out-patient basis

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for symptomatic patients and those in retention were treated as in-patients. Cefuroxime (750 mg) was administered intravenously at the beginning of the procedure. Prostatic dilatation was performed using a purpose-built 35 mm (105 F) balloon (Microvasive Ltd) under intravenous midazolam and pethidine sedation. In view of the poor results obtained using 20 and 25 mm balloons (Gill *et al.*, 1989), the study was not randomised.

The first 12 patients underwent balloon dilatation under fluoroscopic guidance. The bladder was initially catheterised using a 6 F steerable catheter and the balloon exchanged over a guide wire. A radio-opaque skin marker was used to identify the position of the external sphincter prior to balloon inflation. The balloon was inflated for 15 min (Gill *et al.*, 1989). The remaining 42 patients underwent cystoscopic balloon dilatation. A preliminary cystourethroscopy was performed, at which time the appearance of the prostate was noted. A guide wire was then introduced along the sheath of a cystoscope and the balloon was inserted over the wire. Under direct vision the balloon was positioned by aligning the metallic ring at the distal extremity of the balloon just proximal to the external sphincter. The balloon was inflated for 10 min (Castaneda *et al.*, 1987; Reddy *et al.*, 1988).

In all patients a 12 F Foley urethral catheter was inserted at the end of the procedure. This remained *in situ* for 24 h. The initial 29 patients underwent retrograde urethrography before and after dilatation to assess the completeness of commissurotomy. However, it became apparent that a successful outcome was not related to splitting of the prostatic commissures and the procedure was not performed in the remaining 25 patients.

At review 3 months after dilatation all patients underwent symptomatic assessment, using the same questionnaire that had been used before the procedure, free flow rate measurement and inflow and voiding cystometry.

Patients who were both symptomatically improved and unobstructed were followed up symptomatically and urodynamically for 9 months, whilst those who were either obstructed or had obtained no symptomatic improvement were offered a prostatectomy. Patients who were obstructed at 3 months, but who obtained symptomatic improvement, were reviewed symptomatically at 6 and 9 months.

**Table 1** Cystometric Findings in 27 Patients with Bladder Outflow Obstruction Undergoing Balloon Dilatation

| | *Before dilatation Range (mean)* | *3 months after dilatation Range (mean)* |
|---|---|---|
| Flow rate (ml/s) | 3–14 (7.1) | 2–34 (12.4) |
| Detrusor pressure (cm $H_2O$) at peak flow | 50–350 (103) | 34–125 (77.5) |
| Urethral resistance (cm $H_2O/s^2/ml^{-2}$) | 0 5–20 (4.4) | 0.006–15 (2.1) |
| Residual volume (ml) | 5–400 (173) | 6–400 (117) |

## Results

A total of 54 patients aged between 53 and 84 years (mean 74) were treated by balloon dilatation; 25 presented consecutively with acute urinary retention and 29 with cystometric evidence of BOO were taken from the waiting list. Prior to dilatation, 15 of the patients in retention and 20 of those with symptoms of BOO had evidence of detrusor instability on cystometry. In 13 patients the weight of the prostates was estimated at less than 30 g; in 29 it was between 30 and 50 g and in 12 it was over 50 g on digital rectal examination. During dilatation the most frequent symptom was an intense desire to void. However, all but 1 patient failed to recollect this as a result of the retrograde amnesia imparted by the midazolam.

At 3 months, 27 of the 29 patients with BOO were available for follow-up (Table 1); 21 had improved flow rates (mean increase 5.3 ml/s), 19 had a reduced residual volume (mean reduction in volume 70 ml) and 20 showed reduction in detrusor pressures at peak urinary flow (mean reduction 25 cm $H_2O$). Thirteen patients were considered unobstructed on cystometric criteria. All of those who were unobstructed noted improvement in their symptoms; 7 of 20 patients with pre-dilatation detrusor instability had reverted to a stable condition. Of the 14 men dilated for BOO who remained obstructed, 6 were symptomatically improved and 8 unimproved.

Of the 27 patients with BOO, 19 noted an overall improvement in symptoms at 3 months (Table 2). Six patients who noted improvement in their symptoms of frequency, nocturia and urgency remained unstable and 2 patients reverted to stability but were symptomatically unchanged.

Only 6 of the 25 patients with acute retention voided following dilatation and 1 lapsed into

**Table 2** Symptomatic Outcome of 27 Patients with BOO at 3 Months

| | *Improved* | *No change* | *Worse* |
|---|---|---|---|
| Obstructure symptoms | | | |
| Hesitancy (20) | 11 | 8 | 1 |
| Poor stream (27) | 15 | 10 | 2 |
| Incomplete emptying (13) | 4 | 5 | 4 |
| Unstable symptoms | | | |
| Frequency (27) | 15 | 9 | 3 |
| Nocturia (27) | 17 | 7 | 3 |
| Urgency (12) | 7 | 4 | 1 |

Numbers of patients complaining of individual symptoms are shown in brackets.

**Table 3** Correlation between Outcome of Dilatation and a Successful Commissurotomy

| | *Commissurotomy* | *No commissurotomy* |
|---|---|---|
| Cystometric relief of BOO (n = 13) | 6 | 7 |
| Relief of retention (n = 6) | 1 | 5 |
| NO relief of BOO (n = 7) | 2 | 5 |
| NO relief of retention (n = 3) | 2 | 1 |

(n = number of patients undergoing urethrography).

retention before being reviewed at 3 months; 4 of the 5 remaining patients returned for follow-up. Flow rates ranged from 3 to 5 ml/s (mean 3.4) and residual urinary volumes from 5 to 200 ml (mean 114). The mean detrusor pressure at peak urinary flow prior to dilatation was 73 cm $H_2O$ (range 22–140) compared with 77 cm $H_2O$ (range 30–125) following dilatation, whilst the urethral resistance ranged from 1.2 to 9.4 cm $H_2O/s^2/ml^{-2}$ (mean 6.4). No patient was considered unobstructed. Two of the 4 had evidence of detrusor instability prior to dilatation. Following dilatation, 1 showed no evidence of instability on repeat cystometry. Obstructive symptoms were improved in 2 men but symptoms of frequency and nocturia improved in only 1 and worsened in 2 others after the procedure.

Seven of the 9 patients with BOO who were treated radiologically were unobstructed at 3 months with only 6 of the 18 who were treated cystoscopically. Seven of the 9 patients treated radiologically and 12 of the 18 treated cystoscopically obtained symptomatic relief. Of the 25 men with retention, 23 underwent dilatation under direct vision and only 2 under radiological guidance. All patients who voided following dilatation had undergone the procedure under direct vision.

Retrograde urethrography was performed in 29 men and a commissurotomy was demonstrated in 11 (Table 3). In patients with BOO, 6 of 8 men with a commissurotomy were unobstructed, compared with 7 of 12 of those without a commissurotomy. By contrast, in men with retention only 1 of 3 with a commissurotomy voided compared with 5 of 6 without. A successful commissurotomy was not associated with a favourable outcome.

### *Follow-up at 6 months*

Twelve of the 13 patients who were symptomatically improved and without evidence of obstruction at 3 months returned for review at 6 months. In comparison to their pre-dilatation urodynamic parameters (Table 4), 9 still had reduced detrusor pressures and 7 had improved flow rates. Eight patients had reduced urethral resistance and 8 had reduced residual volumes. However, in comparison to follow-up at 3 months, there was a deterioration in urodynamic parameters in nearly all patients. Only 2 had a reduced detrusor pressure; all except 1 had a reduction in flow rate and all had an increased urethral resistance. Residual urinary volumes were reduced in 7 patients. Only 3 of the 12 patients followed up at 6 months remained cystometrically unobstructed. Ten of these patients continued to have overall symptomatic relief in both obstructive and unstable symptoms.

Ten men (6 in the BOO group and 4 with retention) who were obstructed at 3 months, but declined prostatectomy, underwent symptomatic review at 6 months. Five of the 6 with BOO

**Table 4** Cystometric Findings at 3 and 6 Months in 12 Patients Followed up for 6 Months

| | *Before dilatation Range (mean)* | *3 months after dilatation* | *6 months after dilatation* |
|---|---|---|---|
| Flow rate (ml/s) | 3–12 (7.3) | 8–34 (17.4) | 4–25 (11.2) |
| Detrusor pressure (cm $H_2O$) at peak flow | 58–150 (107) | 34–120 (66.8) | 40–150 (77) |
| Urethral resistance (cm $H_2O/s^2/ml^{-2}$) | 0.6–11 (3.6) | 0.05–0.4 (0.3) | 0.14–4.0 (1.3) |
| Residual volume (ml) | 3–350 (105) | 5–200 (42) | 5–150 (33) |

remained improved. Of the 4 patients with retention, 2 still noted an improvement in their obstructive symptoms and 1 lapsed into retention at 4 months.

*Follow-up at 9 months*

The 3 men who were unobstructed at 6 months underwent repeat cystometry and only 2 remained unobstructed. Flow rate values were between 7 and 20 ml/s (mean 14); detrusor pressure at peak urinary flow ranged from 50 to 120 cm $H_2O$ (mean 81) and urethral resistance ranged from 0.1 to 2.5 (mean 1.0). Residual volumes ranged from 25 to 150 ml (mean 45). All patients underwent a review of symptoms. Three men noted increased nocturia and urgency and 1 reported a diminution in his urinary stream. Despite this, 14 patients still felt that their condition had improved following dilatation.

No patient admitted to retrograde ejaculation or incontinence, although 1 complained of loss of erection which he attributed to the procedure. Patients experienced only transient, mild haematuria and none required a blood transfusion. To date, no patient has developed a urethral stricture.

## Discussion

In our previous study (Gill *et al.*, 1989), we demonstrated that dilatation of the prostatic urethra using 20 and 25 mm balloons was unsuccessful in alleviating retention of urine or BOO in the majority of patients. This study assesses the use of 35 mm diameter balloons in 2 similar groups of patients—those presenting with bladder outflow obstruction and those who were catheterised for acute urinary retention.

In 27 patients with BOO we found that 21 had improved free flow rates and 20 reduced detrusor pressure at peak urinary flow. Thirteen patients were considered unobstructed (urethral resistance $<0.5$) at 3 months. By 6 months, however, only 3 remained unobstructed and there was a trend towards pre-dilatation parameters in nearly all patients (Table 4), including the 3 who remained unobstructed. At 9 months, 14 patients still felt improved but only 2 remained unobstructed. It would appear that dilatation offers only temporary relief of obstruction in about 50% of patients but the relief of symptoms may be of greater duration. Balloon dilatation has been advocated as a means of treating patients with BOO on the basis of symptomatic and flow rate improvements (Castaneda *et al.*, 1987, 1988; Klein *et al.*, 1989). In the present study, 19/27 patients (70%) obtained symptomatic relief but only 13 (48%) were considered to be unobstructed. At 6 and 9 months this difference was still more marked, with 55 and 51% respectively achieving an improvement in symptoms; however, only 3 and 2 of 27 (11 and 7%) remained unobstructed at 6 and 9 months respectively. Gill *et al.* (1989) noted a similar disparity between symptoms and objective evidence of improvement. In addition, 6 patients obtained relief of unstable symptoms but still showed cystometric evidence of instability at follow-up. One explanation for these observations may be a placebo response, as described in clinical trials on the treatment of BOO (Castro *et al.*, 1971).

Only 6 of the 25 patients presenting with acute urinary retention voided following the procedure. Two of these have relapsed into retention. Dilatation does not appear to have a role in the treatment of this condition. Two of the men who voided, but were still obstructed, noted improvement in their obstructive symptoms; both were stable pre- and post-operatively. McLoughlin *et al.* (1990) demonstrated that it is often by resolution of the instability associated with BOO that patients gauge the success of their operation. Those who remain obstructed, but have stable detrusors, may feel improved even though their obstruction has not been relieved.

Following dilatation, only 7 of 21 men with instability reverted to stability. This offers further support to our finding that dilatation is not an efficient means of relieving BOO. Turner-Warwick (1979) observed that following efficient relief of obstruction, 75% of men with pre-operative instability may be expected to become stable.

Castaneda *et al.* (1988) suggested that a commissurotomy is required for a successful outcome. In this study we found no such association. In patients with BOO, 6 of 8 in whom dilatation produced a commissurotomy were unobstructed. By comparison, 7 of 12 patients in whom it did not produce a commissurotomy were also unobstructed. In patients who presented with retention, only 1 of 3 with a commissurotomy voided, compared to 5 of 6 of those without. A similar lack of correlation has been reported by Gill *et al.* (1989). The fact that we obtained the same symptomatic response rate as reported in previous studies (Castaneda *et al.*, 1987, 1988; Reddy *et al.*, 1988), where great importance was placed upon producing a commissurotomy, supports the principle that balloon dilatation does not rely upon the production of a commissurotomy to produce relief of BOO or associated symptoms.

In our previous study (Gill *et al.*, 1989), 52% obtained a commissurotomy but only 11% were rendered unobstructed. In the present study, only 41% of patients undergoing retrograde urethrography obtained a commissurotomy but 48% were relieved of bladder outflow obstruction. Again, no correlation was found between a successful commissurotomy and relief of obstruction (Table 3).

It has been suggested that 10 min is the minimum time required to produce dilatation (Reddy *et al.*, 1988). Most studies have employed dilatation for 10 min (Castaneda *et al.*, 1987; Reddy *et al.*, 1988; Klein *et al.*, 1989). In this study, the duration of balloon inflation varied between those performed under cystoscopic guidance (10 min) and radiological guidance (15 min) and we found that a greater proportion of patients dilated for 15 min were rendered unobstructed. It is possible that our results would have been further improved if we had employed dilatation in all patients for 15 min. However, in contrast to our previous study (Gill *et al.*, 1989), where the majority of patients were dilated for 15 min but remained obstructed, it would appear that the size of the balloon has more influence upon a successful outcome than the duration of inflation.

No patient complained of retrograde ejaculation, which suggests that the procedure is not efficient in disrupting the bladder neck mechanism.

This study has shown that 35 mm balloon dilatation alleviates bladder outflow obstruction in approximately 50% of patients for less than 6 months. It cannot be advocated for the relief of obstruction but may have a role in younger men who wish to avoid the risk of retrograde ejaculation. Close urological follow-up is required in such cases in order to detect detrusor decompensation or upper urinary tract embarrassment.

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# Should Urologists wear Spectacles for Transurethral Resection of the Prostate?

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Summary—Contamination of the eyes by irrigation fluid during transurethral resection (TUR) of the prostate was assessed by measuring droplet splashes on to spectacles worn by 2 surgeons. During 30 consecutive operations, droplet splash contamination occurred during every procedure. The number of splashes increased with time.

The use of spectacles during TUR will reduce the risks of eye contamination from droplet splashes and therefore the possibility of transmission of the human immunodeficiency virus from infected patients.

During endoscopic urological surgery, droplet splash contamination of the surgeon's face represents a potential route of transmission of the human immunodeficiency virus (HIV) and hepatitis B. Conjunctival transmission of both HIV and hepatitis B has been reported in health care workers (Gioannini *et al.*, 1988).

The degree of risk of such transmission from patient to surgeon is not fully known, but facial contamination does occur during endoscopic procedures. McNicholas *et al.* (1989) reported that contamination of the eyes and face accounted for 46% (46 of 99 operations) of the contamination occurring in endoscopic surgery.

Urological surgeons need to address this risk, particularly in view of the increasing numbers of HIV-positive patients likely to be encountered in the future.

The risk of hepatitis B infection can be reduced by vaccination. The acquired immune deficiency syndrome (AIDS) is not curable at present and a vaccine to prevent the development of AIDS following HIV seroconversion is not yet available. We investigated droplet contamination of the eyes during transurethral resection of the prostate by examining splashes on spectacles worn by the surgeon. The degree of hazard was then assessed.

## Patients and Methods

Thirty patients undergoing TUR for benign prostatic hypertrophy were studied. Each resection was timed. At the end of the procedure, the number of splashes on the lens surface were counted. Care was taken not to splash the spectacles during scrub-up. J.H.D. wears spectacles normally whilst G.S.M.H. wore safety spectacles with side protectors.

In each case a full length Otis urethrotomy was performed prior to using a 27 F Storz resectoscope. A TUR drape was used with a filter to catch curettings.

## Results

Droplet splashes on the spectacle lenses occurred during all 30 operations, ranging from 1 to 34. As the time of operation increased, so too did the average number of splashes (Table). The higher numbers of splashes occurred more frequently during evacuation of prostatic curettings by means of the Ellick's evacuator in patients with small capacity bladders that required frequent emptying during TUR and when patients coughed or strained under anaesthesia.

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Based on a Poster Demonstration at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

**Table** Frequency of Droplet Contamination

| *Duration of operation* | *<30 min* | *>30 min* |
|---|---|---|
| No of procedures | 18 | 12 |
| No. of splashes | 1–16 | 1–34 |
| Average no | 5 | 9 |

## Discussion

The number of HIV carriers in England and Wales is estimated to be between 36,000 and 148,000 (Wilkie, 1988) and up to 100 million people may be infected by 1993 (Tindall and Landsdowne, 1987).

This study demonstrates that droplet splash contamination occurs in the region of the eyes during TURP. The spectacle lens surface is obviously larger than the palpebral fissure and therefore the conjunctival contamination cannot be directly measured. However, during many TUR operations it is inevitable that some contamination of the conjunctiva will occur.

The identification of HIV-positive patients prior to surgery is made difficult by the fact that laboratory testing may not identify all such patients due to late seroconversion. Also important is the fact that we are not allowed to test for HIV anonymously. The Royal College of Surgeons of Edinburgh (1990), in its recent statement to Fellows on HIV infection and AIDS, stressed that the surgeon should establish the level of risk according to the history, the circumstances of the patient and the nature of the pathology with which he is dealing.

The risks are apparent and its seems likely that unless eye protection is used, it will be only a matter of time before conjunctival transmission of HIV occurs in a urologist. Urological surgeons must decide whether to protect themselves against such risks, either by wearing spectacles during all TUR operations or by gaining expertise in the use of closed circuit television equipment.

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# Orchiectomy versus Oestrogen in the Treatment of Advanced Prostatic Cancer

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Summary—The primary clinical efficacy of orchiectomy and the combination therapy of intramuscular polyoestradiol phosphate 80 mg monthly and oral ethinyl oestradiol 0.15 mg daily was evaluated by progression and cancer mortality rates in a series of 277 prostatic cancer patients representing part of the Finnprostate study. After a follow-up of 5 years there was a significant difference between the groups in terms of progression rate and prostatic cancer deaths. The oestrogen combination was more effective in delaying progression of the disease. The overall mortality rate was similar in both groups. About one-third of the patients were alive after 5 years.

The safety and reliability of orchiectomy in the treatment of advanced prostatic carcinoma have been well established (Merril, 1988) and the procedure is widely used in Finland. It is usually performed as subcapsular orchiectomy and its acceptance by patients is not a problem. The oestrogen treatment commonly used in Scandinavia includes polyoestradiol phosphate, either alone or in combination with ethinyloestradiol (Jõnsson, 1971).

The purpose of the present study was to compare the primary clinical efficacy of orchiectomy and intramuscular polyoestradiol phosphate (PEP) in combination with oral ethinyloestradiol (EE) in the treatment of locally advanced or metastatic prostatic cancer.

## Patients and Methods

The present series of 277 prostatic cancer patients formed part of the 404 prostatic cancer patients included in a Finnish multicentre study (Finnprostate) and diagnosed between February 1979 and December 1982. The diagnoses, exclusion criteria, randomisation design and progression criteria have already been described (Haapiainen *et al.*, 1986).

The current oestrogen group consisted of 146 patients (mean age 72.7 years) and the orchiectomy group included 131 patients (mean age 71.8 years). At the time of diagnosis there were no significant differences between the groups in terms of local extent of tumour (T classification), presence of distant metastases (M classification) or differentiation grade of the malignancy (G classification).

The oestrogen therapy consisted of intramuscular polyoestradiol phosphate (PEP, Estradurin), 160 mg as an initial dose followed by 80 mg monthly. In addition, ethinyloestradiol (EE, Etivex), 1 mg, was given orally for 2 weeks, followed by 150 µg daily. Bilateral castration included either total or subcapsular orchiectomy.

Statistical analysis of proportions was achieved using the $\chi^2$ test and the test for linear trend. Survival analyses were performed by the conventional product limit method and the Cox proportional hazard method. The primary clinical efficacy of oestrogen therapy and orchiectomy was evaluated by progression rates (non-progression was defined as disease-free interval), cancer mortality and cardiovascular mortality after a minimum follow-up of 5 years.

## Results

During the first 5 years, 49 of 131 orchiectomised patients (37%) showed evidence of progression and

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another 12 (9%) had such aggressive disease that they died of disseminated prostatic cancer during the evaluation phase. In the oestrogen group, 25 of 146 patients (17%) showed progression and 22 (15%) died from prostatic carcinoma (Fig. 1). There was a statistically significant difference ($P < 0.05$) between the groups overall, the oestrogen combination being more effective in delaying progression of the disease.

Some differences were observed between the groups in respect of M categories. In both M0 and M1 patients the oestrogen therapy delayed progression more effectively than orchiectomy ($P < 0.005$). The effect of therapy was, however, more pronounced in M1 than in M0 patients (Fig. 2). According to the primary protocol, the treatments were crossed over when progression of disease was verified. In the primary orchiectomy group the total number of deaths during the first 5 years was 86 of 131 patients (66%): 47 deaths from prostatic carcinoma, 24 from cardiovascular and 15 from other causes. In the oestrogen group, 101 of 146 patients (69%) died: 45 from prostatic carcinoma, 35 from cardiovascular and 21 from other causes.

The overall majority is presented in Figure 3. There were no statistically significant differences ($P = 0.45$) in the overall mortality between the primary therapy groups during the 5-year period. About one-third of the patients were still alive.

## Discussion

In the present study, polyoestradiol phosphate in combination with a strong gonadotrophin inhibitor, ethinyloestradiol, delayed prostatic cancer progression more effectively than orchiectomy. This difference had already been noted following 2 years' follow-up by Haapiainen *et al.* (1986). A possible explanation could be the existence of non-equalising differences between the groups at the time of diagnosis, although small, insignificant, random variations in the local extent of the tumour, differentiation grade of malignancy or the presence of metastases hardly explain this. In fact, the oestrogen group exhibited more bone metastases at the time of diagnosis (55%) than the orchiectomy group (45%). The mean age of the patients was also similar. Co-operation within the Finnprostate study

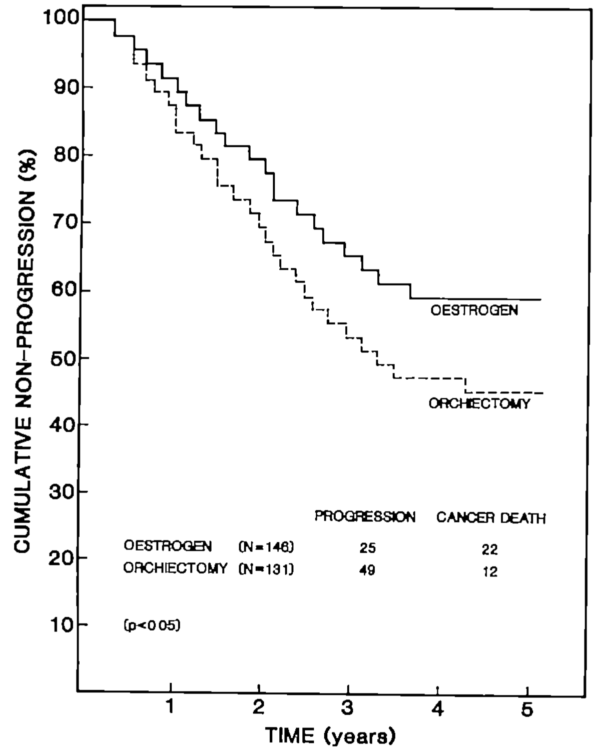

**Fig. 1** Cumulative non-progression curve for patients with prostatic carcinoma treated by oestrogen or orchiectomy.

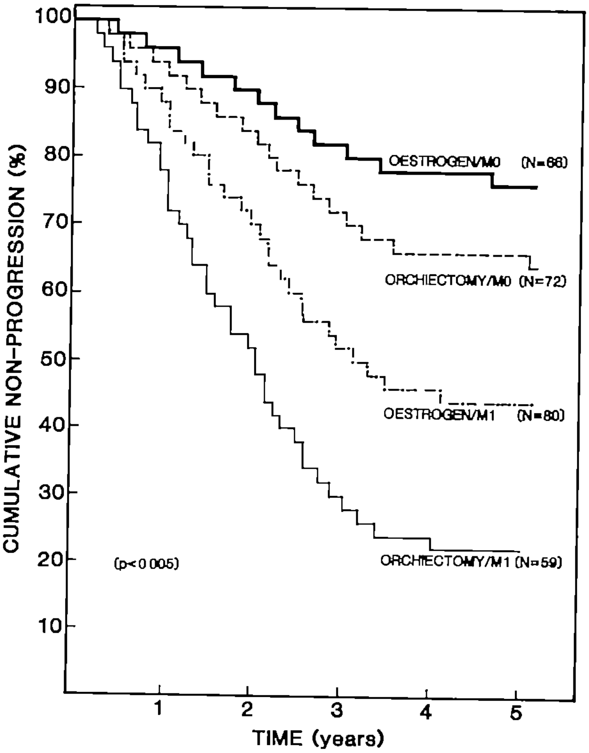

**Fig. 2** Cumulative non-progression curve for M0 and M1 prostatic cancer patients treated by oestrogen or orchiectomy.

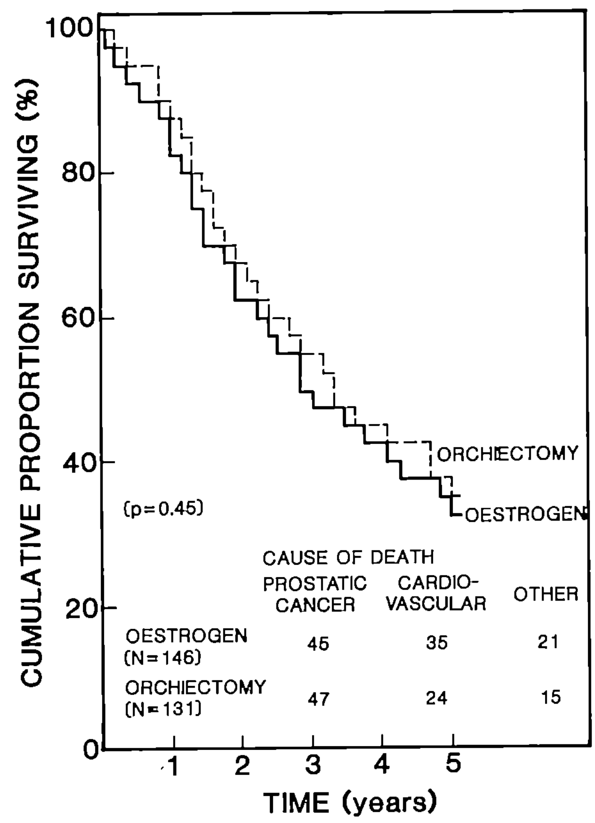

**Fig. 3** Cumulative survival of prostatic cancer patients treated by oestrogen or orchiectomy.

group has been good; its composition has not changed during the 10 years of the study and the same criteria have been applied throughout. As soon as progression was confirmed, the primary treatments were crossed over, which is also an indication that in each individual case the response to primary therapy was carefully evaluated.

The combination of intramuscular PEP (80 mg monthly) and oral EE (0.15 mg daily) reduces serum testosterone to castration level. This combination is more effective in reducing testosterone levels than is PEP alone at a dosage of 160 mg every 4 weeks (Carlström *et al.*, 1989). It is possible that the beneficial effect of oestrogen is based not only on reduction of the androgen concentration but also on a simultaneous direct cytotoxic effect (Susan *et al.*, 1976). In both M0 and M1 patients the oestrogen therapy was more effective than orchiectomy in delaying progression, the effect being more pronounced in the M1 patients. Prostatic carcinomas are composed of a heterogeneous population of androgen-dependent and androgen-independent cells (Coffey and Baals, 1981). After orchiectomy the level of serum testosterone drops immediately, which may allow the androgen-independent tumour cells to continue growing, and the cytotoxic effect of oestrogen therapy is increased through inhibition of the growth of this androgen-independent cell line.

Although the combination of PEP and EE delayed cancer progression more effectively than orchiectomy, the risk of early phase cardiovascular side effects was noted in our 2-year analysis (Haapiainen *et al.*, 1986) and this has been confirmed in other studies (Daehlin *et al.*, 1986; Lundgren *et al.*, 1986). There is evidence that these side effects are specifically related to oral administration, which produces a marked oestrogenic impact during first-pass metabolism, with a resultant increase in liver-synthesised coagulative and fibrinolytic proteins (Damber *et al.*, 1979; von Schoultz *et al.* 1989). Clinically this may be reflected by the fact that most thromboembolic complications in the oestrogen-treated patients occurred during the first year of treatment (Haapiainen *et al.*, 1986; Aro *et al.*, 1988). In the present study there were more deaths from cardiovascular disease in the oestrogen group (24%) than in the orchiectomy group (18%) during the first 5-year period. Half of these deaths in the oestrogen group and one-third in the orchiectomy group occurred during the first 2 years; thereafter the difference was less marked.

The cumulative all-cause mortality rates were similar in both groups during the 5-year period. About one-third of the prostatic cancer patients remained alive. The combination of PEP and EE seemed to delay cancer progression more effectively than orchiectomy. Clinically, delay in progression means a symptom-free period for a single patient and is of importance before permanent hospitalisation. In the present study, this favourable response was emphasised in patients with metastases at the time of diagnosis. Orchiectomy remains an important method of treating patients with locally advanced or metastatic prostatic cancer. If combination therapy with PEP and EE is used, its risk-benefit ratio should be evaluated individually in respect of cardiovascular side effects and the selection criteria, in terms of earlier cardiovascular problems, should be strict.

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# Urological Manifestations of HIV-related Disease

## A Case of AIDS-associated Testicular Seminoma, Kaposi's Sarcoma and Possible Intracranial Lymphoma

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Summary—A wide variety of pathologies afflicting the genitourinary tract can be displayed by patients infected with the human immunodeficiency virus (HIV), including both infective and neoplastic conditions. Treatment can often be offered for such conditions using a combination of therapeutic approaches. These conditions should be looked for specifically in patients with HIV infection as treatment may improve their quality of life. A case is presented of a testicular seminoma (appearing in association with an intracranial mass and Kaposi's sarcoma) in a male patient with the acquired immune deficiency syndrome (AIDS); he made a good response to orchiectomy and radiotherapy for his seminoma.

A short review is also given of the range of HIV-associated genitourinary pathologies which have been described to date.

Patients infected with the human immunodeficiency virus may manifest a wide range of unusual malignant tumours (Monfardii *et al.*, 1989), some of which are treatable by surgical means. A case is presented of a 41-year-old homosexual male with AIDS who during the course of his illness developed at least 2 and possibly 3 solid tumours, including a testicular seminoma which was treated surgically.

### Case Report

The patient first presented in November 1985 with night sweats and significant weight loss, but was otherwise well. He was diagnosed as being seropositive for antibodies to HIV. In March 1986 he developed progressive Kaposi's sarcoma (KS), affecting his thorax, limbs and palate, for which he was treated with interferon. A few months later he noted an enlarged left testis which was confirmed during routine physical assessment. At orchiectomy, a seminoma was encountered and post-operative radiotherapy was commenced. Interferon was withdrawn, the KS subsequently being treated with etoposide. At this time atypical mycobacteria were observed in his bone marrow. In September 1986 there was a sudden, severe deterioration in his condition, culminating in collapse associated with semi-coma, hypertonia, hyper-reflexia and some neck stiffness. A cranial CT scan revealed a space-occupying lesion with surrounding oedema. Although the underlying pathology of this was uncertain, the lesion's appearance was typical of lymphoma of the non-Hodgkin type rather than the exceedingly rare intracranial KS (Levy *et al.*, 1985; Amazon and Rywlin, 1988) or an abscess. Mannitol and dexamethasone were commenced and neurosurgical advice was sought; it was felt that no useful treatment could be offered for intracranial lymphoma and he was treated empirically with ketoconazole and pyrimethamine and sulphadoxine to cover the possibilities of a fungal or toxoplasma abscess. Despite these measures his condition deteriorated and he died. Unfortunately no autopsy was possible.

### Discussion

Although testicular tumours have occasionally been observed in HIV-infected patients (Levine, 1988; Monfardii *et al.*, 1989), its occurrence here with KS and possible non-Hodgkin's lymphoma makes this

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case rather remarkable and underlines the increased propensity of these patients to an array of diverse neoplastic manifestations. Although the patient was HIV-seropositive, this did not prevent a surgical approach being adopted to his treatment.

This patient's experiences reinforce the view that a full consideration of the genitourinary system is extremely important in a complete appraisal of the potential manifestations of HIV-related disease. Genital ulceration has been reported to be a feature of the transient acute HIV-related seroconversion illness which occurs in about 25% of patients 6 days to 6 months following infection with HIV (Biggar *et al.*, 1986). Testicular atrophy and decreased spermatogenesis may also occur very early on in the natural history (Chabon *et al.*, 1987; Harami, 1989). Later, as the disease progresses, several other problems may be encountered.

Some are conditions which may occur in the non-HIV-infected patient but are in general more severe and/or more difficult to treat adequately in the HIV-infected patient; these include genital herpes (Whitley *et al.*, 1984), genital warts resulting from infection with the human papillomavirus (Cockerell and Friedman-Kein, 1989), syphilis, gonorrhoea, *Chlamydia trachomatis*-related urethritis (Koehler and Chaisson, 1989), candidiasis and other sexually transmitted infections. HIV-associated genitourinary tuberculosis with all its potential urological complications is again increasing in prevalence in some parts of the world (Morais de Sa *et al.*, 1989; Muller *et al.*, 1989; Schecter, 1989).

More unusual genitourinary conditions have also been described. These include cytomegalovirus epididymitis (Randazzo *et al.*, 1986), testicular toxoplasmosis (Catterall *et al.*, 1986; Nistal *et al.*, 1986), cryptococcal prostatitis (Lief and Sarfarazi, 1986), renal coccidioidomycosis (Threlkeld and Dismukes, 1989), renal salmonellosis (Koehler and Chaisson, 1989) and penile amoebiasis (Petersen, 1989), which may be mistaken for a penile carcinoma (Thomas and Antony, 1976). Renal involvement with a variety of species of atypical mycobacteria has also been described (Boldt *et al.*, 1989; Damiano *et al.*, 1989). Urinary retention may result from the development of AIDS-associated progressive radiculopathy (Eidelberg *et al.*, 1986). The penis may be a site for Kaposi's sarcoma (Seftel *et al.*, 1986; Amazon and Rywlin, 1988). Surgical biopsy may be essential to achieve a diagnosis in many of these conditions.

Many of the lesions described here, either neoplastic or infective in origin, are now potentially amenable to treatment and the surgeon may become involved both in the diagnosis (biopsy-taking) or treatment (*e.g.* resection, abscess drainage). Accordingly, regular careful examination of the testes and genitourinary tract should occupy a high priority in the general assessment of the HIV-infected patient (Clement, 1989).

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# Sperm Retrieval by Electro-ejaculation

## Preliminary Experience in Patients with Secondary Anejaculation

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Summary—Twelve patients with spinal cord injury and 2 diabetics with secondary anejaculation underwent 26 sessions of electro-ejaculation, using a technique which has previously been popular only in veterinary medicine. Ejaculate was obtained on 21 occasions. Semen quality was adequate for cryostorage on 9 occasions (8 patients); on 8 occasions (5 patients) it was used for immediate artificial insemination of the partner. To date, there has been 1 pregnancy resulting in a live birth.

Natural ejaculation as the culmination of a sexual act occurs in men with spinal cord injury in between 4 and 10% of those with complete lesions. The incidence decreases with higher neurological levels (Brindley, 1984). This fact, combined with the frequent occurrence of urinary tract infection and epididymitis, has resulted in very low fertility in this usually young population. Testicular biopsy in men with high cord lesions often reveals retarded spermatogenesis and interstitial fibrosis. Patients with lower motor neurone lesions usually have normal spermatogenesis (Engel, 1987).

Brindley (1984) demonstrated that application of a powerful vibrator to the base of the penis resulted in ejaculation in approximately 60% of patients with established cord lesions. Repeating this procedure at regular intervals could result in an improvement in semen quality (Beretta *et al.*, 1989). In the remaining patients a further 60% have been found to respond successfully to electro-ejaculation. This is a practice derived from veterinary medicine which was first applied to man in 1948 (Horne *et al.*, 1948) but has only recently achieved any degree of success in man. Brindley (1984) succeeded in obtaining either an antegrade or retrograde ejaculate in 50 of his 84 patients and subsequently reported 11 pregnancies and 9 live births.

The "Brindley" technique consists of a specially moulded silicone rubber finger glove into which are mounted 3 small electrodes. This is inserted into the rectum so that the electrodes lie in a lateral position in the pelvis against the rectal mucosa. Stimulation is produced by pulses of direct current of short duration (100 μs) and constant frequency (10, 15 or 30 Hz) in order to stimulate the myelinated efferent nerves close to the rectum (Brindley, 1981).

It is noteworthy, however, that results similar to those of Brindley have not been reported by other workers and in our experience there has been disillusionment with this technique.

Halstead *et al.* (1987) described a fundamentally different, though conceptually older, technique; the application of a sinusoidal alternating current with a large rectal probe applied anteriorly in the rectum. This technique had been used successfully for many years by one author (S.W.J.S.) in his work on the breeding of endangered non-human mammalian species.

We have assessed the feasibility of using this different technique of electro-ejaculation in a group of anejaculatory subjects and their partners in the context of a fertility clinic with laboratory facilities immediately accessible for preparing sperm.

## Patients and Methods

Table 1 summarises the details of the 14 patients who underwent electro-ejaculation in 26 separate sessions. There were 12 patients with spinal cord injuries, all of whom had previously failed to

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**Table 1** Details of Patients

| *Patient* | *Age (years)* | *Level of injury* | *Complete/ incomplete* | *Duration of injury (years)* |
|---|---|---|---|---|
| A | 32 | T10 | C | 19 |
| B | 28 | C5 | C | 6 |
| C | 37 | Diabetic | | 17 |
| D | 25 | T10 | C | 2 |
| E | 27 | T6 | I | 9 |
| F | 39 | T6 | C | 13 |
| G | 45 | T10 | C | 22 |
| H | 35 | Diabetic | | 8 |
| I | 39 | C5 | C | 5 |
| J | 30 | T10 | I | 8 |
| K | 26 | T7 | C | 10 |
| L | 34 | T9 | C | 3 |
| M | 41 | T6 | C | 4 |
| N | 46 | C5 | C | 14 |

ejaculate using the "Brindley" technique of stimulation; 11 of these patients were married and anxious to conceive a child. A further 12 patients with diabetes mellitus and secondary anorgasmy underwent electro-ejaculation under general anaesthesia. All patients gave informed consent to the procedure.

A size 16 catheter was passed aseptically into the bladder and the bladder emptied and washed out with Ham's F 10 culture solution. Patients with spinal cord lesions at or above the sixth thoracic level were given a prophylactic dose of glyceryl trinitrate or nifedipine (20–40 mg) sub-lingually at least 20 min prior to the procedure in order to reduce the risk of autonomic dysreflexia. With the patient lying in the right lateral position, adequately protected by cushions, preliminary proctoscopy was first performed to check the appearance of the rectal mucosa.

The stimulatory rectal probe was then inserted with pressure applied to bring it into good contact with the anterior rectal wall. The probe is shown in Figure 1 and consists of a solid cylindrical rod of PVC, $1\frac{1}{8}$ or $1\frac{1}{4}$ inches in diameter, into which are inserted 3 linear steel electrodes along the long axis of the probe. Also incorporated in the probe is a thermocouple capable of recording the temperature of the central electrode. A sinusoidal isolated alternating current was applied at 50 Hz by the operator and delivered in bursts of increasing intensity, each lasting several seconds. The intensity was gradually increased (up to 35 V; current up to 900 mA) in order to achieve erection and eventual ejaculation. Whilst the operator controlled the application of the rectal stimulus a further individual monitored the patient's blood pressure. If the diastolic blood pressure rose above 200 mmHg the procedure was abandoned until the pressure dropped. Another person sat in front of the patient holding a collecting jar to catch the ejaculate and simultaneously massage the urethra. After an antegrade ejaculate had been achieved, or alternatively 100% erection had occurred with several repeated bursts of stimuli, the bladder was recatheterised and again washed out with Ham's F 10 solution to obtain any retrograde ejaculation. Finally, proctoscopy was repeated to observe any change in appearance of the rectal mucosa resulting from stimulation.

Sperm was analysed using standard techniques (World Health Organisation, 1987b). Sperm was prepared for artificial insemination using centrifugation and resuspension in a solution of 10% wife's serum supplemented by Hams F 10 solution. The exact technique depended on the quality of the sample. Particularly good samples might have been allowed to swim up into Hams F 10 after centrifugation, although none in this series was considered to be that good. Samples were also prepared for cryostorage using a standard technique with egg yolk and glycerol (Richardson, 1976).

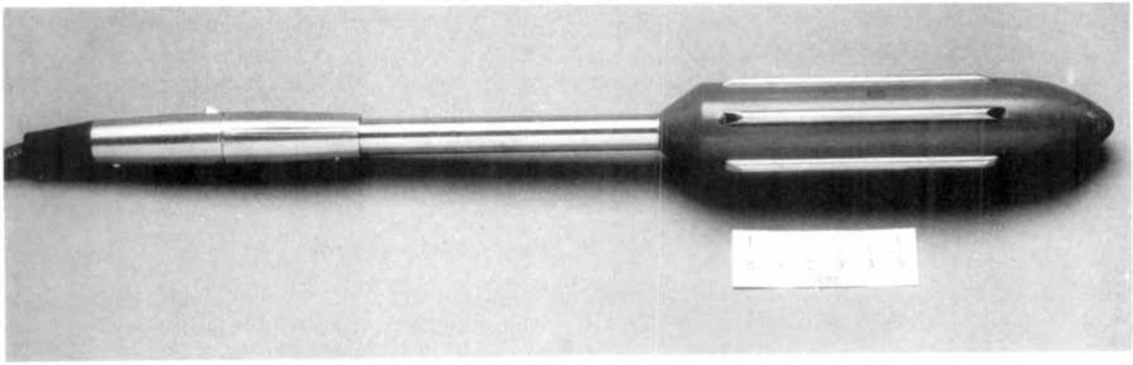

**Fig. 1** Probe used for electrostimulation of anterior rectal wall.

## Results

Ejaculate was obtained from 11 spinal cord patients and 1 diabetic patient in 21 of 26 sessions (Table 2). The ejaculate was antegrade in 11 patients and also retrograde in 7. The immediate motile densities of the semen specimens are recorded in Figure 2.

The technique failed to produce an ejaculate in 2 patients. The first was a C5 tetraplegic in whom rectal stimulation produced a rapid rise in blood pressure (220/130) and the procedure was abandoned to avoid the risk of autonomic dysreflexia. One diabetic patient with a sacral autonomic neuropathy also failed to ejaculate. In a further 2 patients (3 stimulation sessions) who were paraplegic at T8 and T10 respectively, ejaculate was obtained but no sperm were identified in the semen specimen.

Details of sperm quality are shown in Table 2. Nine semen samples were immediately prepared for cryostorage. In 8 patients the semen was used for immediate artifical insemination of the wife.

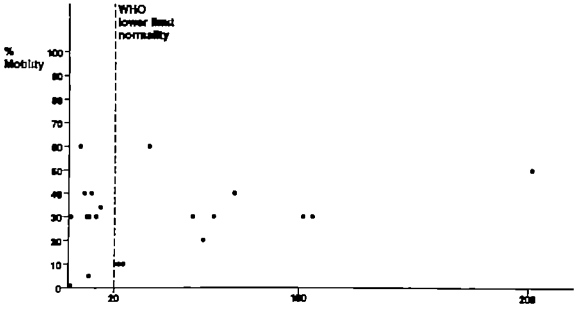

Fig. 2 Immediate sperm motile densities in relation to World Health Organisation standards.

Two other wives have subsequently begun ultrasound tracking for ovulation with the intention of artificially inseminating them at the appropriate time. One wife achieved pregnancy from an entirely retrograde ejaculate produced by a patient with incomplete T 10 paraplegia of 8 years' duration,

**Table 2** Characteristics of Ejaculate

| *Patient* | *Antegrade or retrograde* | *Volume (ml)* | *% Progressive motility* | *Sperm concentration (million/ml)* | *Usage of semen* |
|---|---|---|---|---|---|
| A | A+R | 5.5 | 60 | 5 | Cryostored |
| | | | 40 | 10 | AIH |
| B | A+R | Drop | 40 | 7 | Cryostored |
| | A+R | Drop | 30 | 8 | AIH |
| | A+R | Drop | 30 | 102 | AIH |
| C | A+R | 2 | 10 | 24 | Cryostored |
| | A+R | 1.4 | 30 | 106 | Wife on US tracking |
| D | A+R | 2 | 30 | 9 | AIH |
| | A+R | 9 | 30 | 1 | AIH |
| E | A | 2 | 30 | 12 | Not trying |
| F | A+R | 1 | 20 | 59 | Cryostored |
| | A+R | 1.6 | 0 | 0.02 | |
| G | A | 1 | 0 | 0 | |
| H | Nil | | | | |
| I | Nil | | | | |
| J | R | | 35 | 14 | Cryostored |
| | R | | 30 | 54 | AIH Pregnancy resulting in live birth |
| K | Nil | | | | |
| | A | 3.7 | 0 | 0 | |
| L | A | 3 | 40 | 72 | Cryostored |
| | A | 2.5 | 30 | 63 | AIH |
| | A | 1 | 60 | 35 | Cryostorage + US tracking of wife |
| | A | | | | AIH |
| M | A | 2 | 50 | 260 | Cryostored |
| N | A+R | 0.5 | 5 | 9 | Cryostored |
| | A+R | 2 | 10 | 22 | |

and this resulted in the birth of a healthy boy at full term. The immediate semen sample in this case showed 54 million sperm/ml with 30% motility.

## Discussion

The parameters of electrostimulation used by Brindley (1981) carry the lowest theoretical risk of electrolytic or thermal damage to the rectal mucosa. Techniques using sinusoidal alternating current have, however, been used for nearly 50 years in veterinary practice both in establishing animal models of human disease and in work to save endangered mammalian species (Ball, 1976). With the assistance of an expert with considerable experience of such veterinary work (S.W.J. Seager), we have found this technique to be successful where the "Brindley" technique has previously failed. We have observed no significant thermal damage to the rectal mucosa in this series. No patient complained of pain, though the lower limb spasm experienced by some patients is considerable and causes discomfort. One further disadvantage with the "Brindley" technique is that it requires efferent nerves below the level of the neurological lesion to be intact. The "Seager" technique works in patients with both suprasacral and sacral lesions.

This implies that it relies not on nerve-mediated stimulation but on direct stimulation of the muscle itself, presumably the seminal vesicles. However, unpublished work by S.W.J. Seager suggests that this technique is not successful during the "spinal shock" phase of recovery from cord injury.

The majority of our patients ejaculated retrogradely, but this was not a problem because the bladder was washed out immediately prior to and after stimulation with Ham's F 10 solution in order to obtain the retrograde ejaculate. Fluid intake had been restricted for 12 h prior to the procedure in order to reduce urine output and urine contamination of retrograde semen. Other patients have also been given bicarbonate tablets in order to raise the pH of the urine and further reduce the spermicidal effect of any urine which is present during the procedure (J.P. Macdermott, personal communication). The levels of motility and sperm concentration achieved in this short series were below the lower limit of normal accepted by the World Health Organisation (1987a) in 50% of patients. However, such levels of motile density are still capable of leading to pregnancy (Hargreave and Elton, 1986). We have no evidence from this short study of any tendency for sperm quality to improve with repeated stimulation.

In conclusion, we found the "Seager" technique to be successful in patients with spinal cord injury and diabetes mellitus where the "Brindley" technique had failed. We believe that full and close liaison with an "assisted conception" or fertility service is vital to the success of such a programme.

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# The Growing Teratoma Syndrome

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Summary—Thirteen patients with metastatic non-seminomatous germ cell tumours and enlarging metastases consisting of teratoma differentiated only were identified. Patients were managed with surgical resection soon after the growing lesions were documented. Surgical morbidity was minimal and 12 patients are alive (10 are disease-free) at a median follow-up of 28 months.

The introduction of platinum-containing combination chemotherapy has dramatically improved the survival of patients with metastatic non-seminomatous germ cell tumours (Loehrer *et al.*, 1988). Once tumour markers have returned to normal following a course of chemotherapy it is accepted practice to consider resection of residual masses.

Patients with residual masses form 2 main groups. Those with residual masses and rising tumour markers have progressive disease and in general are treated with further chemotherapy. More common, however, are patients with residual masses and normal tumour markers, whose resected specimens show necrosis and/or fibrosis, teratoma differentiated, persistent tumour (malignant teratoma undifferentiated, yolk sac tumour, choriocarcinoma, seminoma) or any combination of these.

Enlarging masses associated with substantially elevated or rising tumour markers usually parallel progressive or recurrent disease and the outlook may be poor. However, in a number of cases with normal or falling tumour markers such masses have proved to consist of teratoma differentiated and this has been termed the "growing teratoma syndrome" by Logothetis *et al.* (1982).

To date 26 such cases have been described in the literature (Hong *et al.*, 1977; Carr *et al.*, 1981; Logothetis *et al.*, 1982; Levitt *et al.*, 1985; Lorigan *et al.*, 1988; Tonkin *et al.*, 1989), although other series (Husband *et al.*, 1982; Tait *et al.*, 1984) have almost certainly contained similar examples. However, the clinical situations in which the syndrome may occur and the precise frequency with which it arises have not been fully documented.

This report describes 13 cases of the growing teratoma syndrome seen at one institution over a period of 13 years. The clinical, radiological and histological features are presented and a policy for the recognition and management of this syndrome is outlined.

## Patients and Methods

The case notes of patients with metastatic testicular germ cell tumours managed in the CRC Wessex Regional Medical Oncology Unit between 1977 and 1990 were reviewed and patients fulfilling the following criteria for the growing teratoma syndrome were studied in detail:

1. Radiological evidence of enlargement of metastases during or after chemotherapy.
2. Subsequent surgical resection.
3. Predominant teratoma differentiated in resected specimen.

A total of 131 patients with metastatic non-seminomatous germ cell tumours were treated with chemotherapy in this unit during the period under study and 10 of these patients (7.6%) satisfied the criteria for the growing teratoma syndrome. An additional 3 patients received their initial chemotherapy at other centres but their surgical management and subsequent follow-up has been in

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**Table 1** Clinical Details

| *Patient no.* | *Age (years)* | *Tumour markers at surgery* | *Time from end of chemotherapy to surgery (months)* | *No of chemotherapy cycles* | *Survival (months)* | |
|---|---|---|---|---|---|---|
| | | | | | *After surgery* | *Overall* |
| 1 | 30 | N | 1 | 4 | 1+ | 5+ |
| 2 | 35 | N | 1 | 6 | 5+ | 11+ |
| 3 | 22 | N | 1 | 4 | 7+ | 11+ |
| 4 | 22 | AFP11 | * | 6 | 12 | 15 |
| 5† | 27 | N | 1 | 9 | 4+ | 16+ |
| 6 | 17 | HCG 8 | 2 | 5 | 20+ | 24+ |
| 7 | 24 | N | 1 | 4 | 20+ | 28+ |
| 8 | 25 | N | 16 | 6 | 11+ | 32+ |
| 9† | 21 | AFP 19 | 25 | 6 | 9+ | 37+ |
| 10 | 40 | N | 1 | 6 | 23+ | 42+ |
| 11 | 20 | N | 5 | 4 | 37+ | 46+ |
| 12† | 46 | N | 23 | 12 | 21+ | 72+ |
| 13 | 47 | N | 2 | 4 | 68+ | 82+ |

* Patient had surgery during planned chemotherapy.
† Chemotherapy given at other centre
Normal ranges: AFP <10 iu/l; BHCG <4 iu/l

Southampton. The clinical details of all 13 patients are displayed in Table 1. The median age was 25 years (range 17–47).

All patients were staged at presentation with physical examination, chest X-ray (CXR), full blood count, biochemical profile, serum beta-human chorionic gonadotrophin (BHCG) and alpha-fetoprotein (AFP) levels and computed tomography (CT) scanning of the retroperitoneum and chest. Patients were staged according to the Royal Marsden Hospital staging classification (Peckham *et al.*, 1979). Advanced disease (stage III or IV) was present in 7 of the 13 patients at presentation.

Eight patients received the BEP regimen (Peckham *et al.*, 1983); 3 patients were treated with PVB chemotherapy (Einhorn *et al.*, 1977); 1 patient (no. 5) was initially treated at another centre with the POMBACE regimen (Newlands *et al.*, 1983) and 1 further patient (no. 12) received a variety of regimens at another centre before transfer. All patients received at least 4 cycles of cisplatin-containing chemotherapy.

The histology of 12 of the 13 primary tumours and all of the resected metastases was reviewed and classified according to the criteria of the British Testicular Tumour Panel (Pugh, 1976) and the World Health Organisation. An average of 6 sections (range 3–9) was available from the primary testicular tumours and 10 sections (range 5–20) from the metastases; 1 patient underwent orchiectomy after chemotherapy.

The relevant radiological investigations were reviewed and serial changes in the dimensions of metastatic lesions on CT scanning were recorded. All CT examinations in Southampton were performed using 8 mm slice thickness. Sections were at 10 and 16 mm intervals through the thorax and abdomen respectively. The maximum diameters of the largest nodal mass were recorded at each major site. If the nodes were not separable by fat planes the total mass was measured. The attenuation numbers of metastases were recorded and the presence of subjective cystic change was noted.

Many of the masses were irregular in contour and changed shape on serial scans. It was therefore felt that the area of the mass, at any given area, would most accurately represent the changes in size. Areas were calculated by drawing around the mass using the standard computer statistics software available on the CT machine. These measurements were not available on 3 patients scanned outside Southampton. In view of the irregularity of masses and the difficulty in measuring their longitudinal extent it was considered that formulae for calculating tumour volume from measured dimensions were not valid.

## Case Reports

*Patient no. 3.* This 22-year-old man presented with a 4-month history of induration of the right testis and backache for 3 weeks. AFP and BHCG were both elevated at 5910 and 137 iu/l respectively. Orchiectomy revealed a 9 cm tumour which was predominantly made up of yolk sac tumour with small areas of teratoma differentiated and necrosis (Fig. 1). Staging revealed a 10.3 × 10.1 cm retroperitoneal mass and 6 cycles of BEP chemotherapy were planned because of the tumour bulk. During chemotherapy the tumour markers returned to normal but clinically the abdominal mass enlarged (confirmed on CT). Surgery was performed after 4 cycles and an 18 cm cystic tumour invading the aorta and psoas muscle was found. Resection was achieved with some difficulty and a section of the abdominal aorta was replaced with an 18 × 25 mm aortic graft. Histology showed teratoma differentiated with prominent cystic change and immature areas (Fig. 1). Follow-up scans 3 and 6 months after surgery showed stable cystic retrocrural disease. Subsequent scans revealed enlarging disease and coincided with the development of severe back pain. A combined thoraco-abdominal procedure was performed; retrocrural and recurrent intra-abdominal disease was resected (teratoma differentiated only), the abdominal aortic graft was replaced but the patient died 48 h after surgery from uncontrollable haemorrhage; 12 months had elapsed since his first laparotomy.

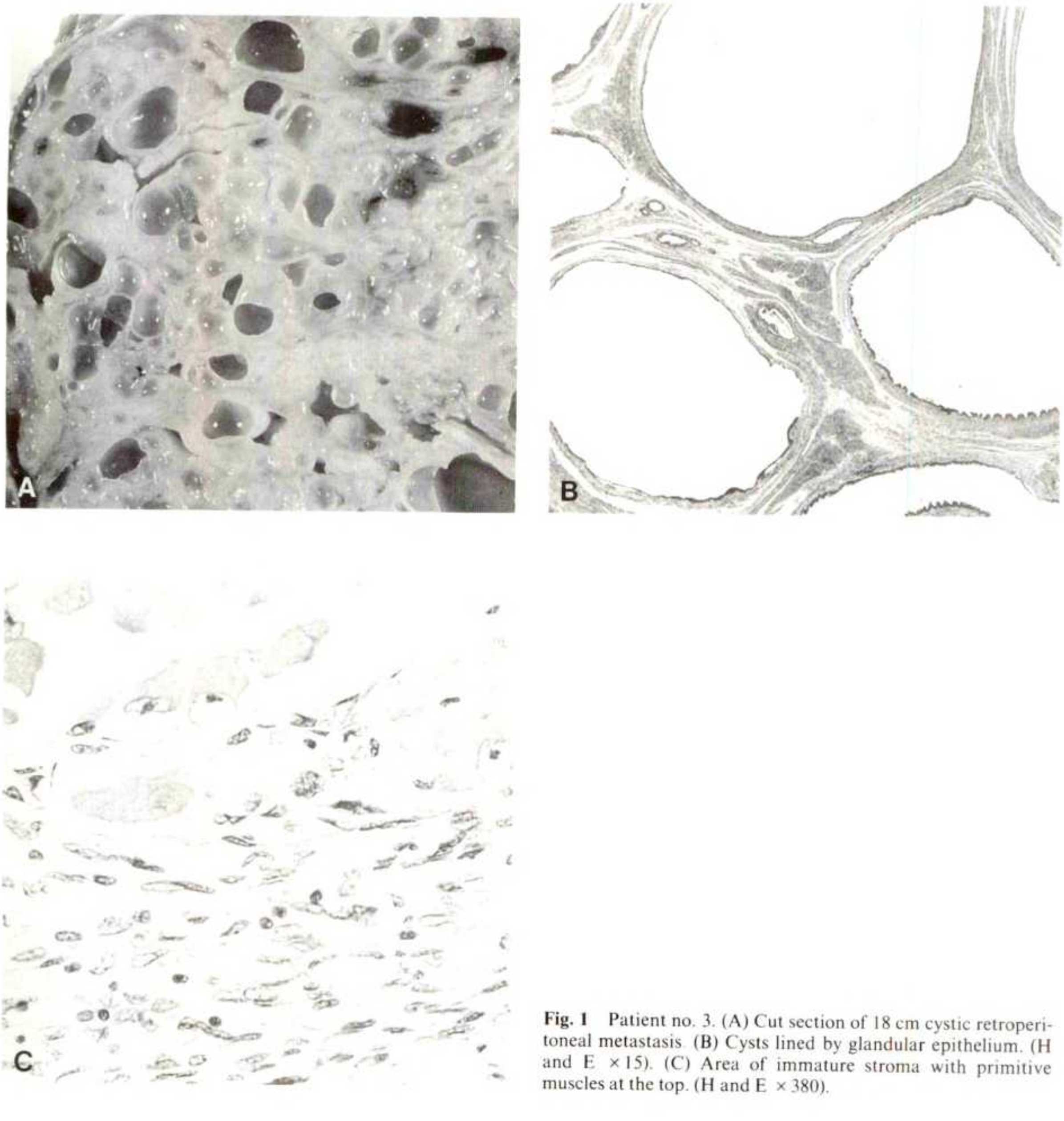

**Fig. 1** Patient no. 3. (A) Cut section of 18 cm cystic retroperitoneal metastasis. (B) Cysts lined by glandular epithelium. (H and E × 15). (C) Area of immature stroma with primitive muscles at the top. (H and E × 380).

*Patient no. 5.* This 17-year-old male presented with a 4-month history of testicular enlargement. AFP and BHCG were elevated at 8102 and 776 iu/l respectively. At orchiectomy a 3.5 cm tumour was found which histologically was a mixture of yolk sac tumour and malignant teratoma undifferentiated (MTU). CT scanning revealed a 10.2 × 9.2 cm para-aortic mass causing a left hydronephrosis and displacing the aorta anteriorly (Fig. 2) and 5 small sub-pleural chest metastases. Tumour markers fell on BEP chemotherapy and after 2 cycles repeat CT showed reduction in size of the para-aortic mass. After 4 cycles of BEP a further CT scan revealed a significant increase in the para-aortic mass (Fig. 2), although tumour markers were almost normal. At surgery a 13 cm cystic mass was found adherent to and displacing the ureter. The mass was freed from the ureter and resected. Histology of the mass showed teratoma differentiated and a microscopic focus of adenocarcinoma. Two further cycles of BEP were given after surgery and the patient is alive and well and in complete remission 20 months after surgery and 24 months from presentation.

## Results

### *Radiology*

CT scanning clearly delineated the growing metastases in 12 patients with CXR documenting the serial changes in the remaining patient (Table 2). In cases where the increase in diameter of metastases was marginal the change in cross-sectional area was often more marked. In all 12 patients studied by CT scanning the metastases became subjectively more cystic and in 9 of the 10 patients with serial scans at Southampton a decrease in the mean attenuation number was observed (data not shown).

### *Pathology: primary tumours*

No slides were available from the patient who underwent orchiectomy after chemotherapy. Of the remaining 12 cases, 10 were classified as malignant teratoma intermediate (MTI–3 combined with seminoma) and 2 as MTU (both with seminoma). In 3 cases the only non-seminomatous high grade component was yolk sac tumour and this was also a prominent element in a further 2 patients who had only small areas of undifferentiated teratoma. In 5 of the 10 cases which included teratoma differentiated, immature elements were prominent. In one case, sheets of tumour with morphological features of rhabdomyosarcoma had developed in such an area of immature teratoma.

### *Metastases*

The resected metastatic deposits ranged in maximum size from 5 to 18 cm (mean 10.5) and all

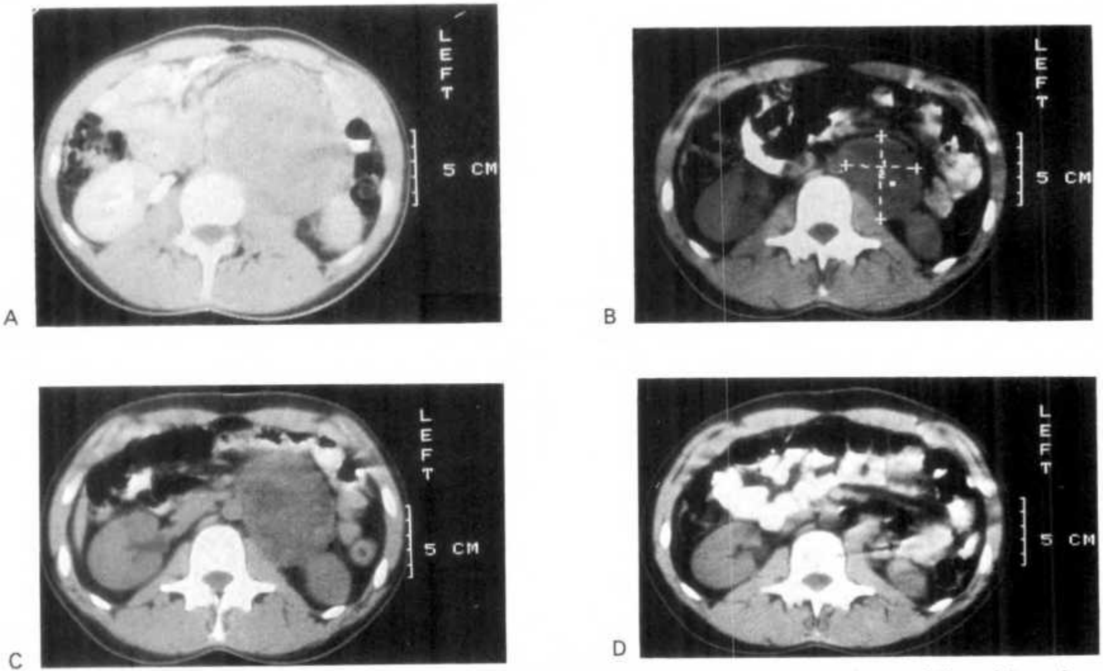

**Fig. 2** Patient no. 5. Serial abdominal CT scans showing initial decrease in retroperitoneal mass followed by enlargement. (A) presentation. (B) After 2 cycles BEP. (C) After 4 cycles BEP. (D) After surgery.

**Table 2** Radiology: Changes in Dimensions of Metastases during Treatment

| | | *Max. diameter (cm) (area in $cm^2$)* | | |
|---|---|---|---|---|
| *Patient no.* | *Site* | *Before chemotherapy* | *After chemotherapy* | *Before surgery* |
| 1 | RP | 2.2 | 3.3 (8.5) | † |
| 2 | Lung | 1.0 | 1 0 | 1.0 |
| | RP | 4.3 | 9.5 | 11.9 |
| 3 | RP | 4.2 (10.8) | 5.4 (20.4) | † |
| 4 | RP | 10.3 (78 4) | 11 4 (93.7) | † |
| 5* | Lingula | 1.0 | nil | 1.0 |
| | Mediastinum | < 1.0 | 2.0 | 3.0 |
| | RP | 6.0 | 6.0 | 9.8 |
| 6 | RP | 10.2 (71.3) | 5.8 (25.8) | 8 3 (45.2) |
| 7 | RP | 2.8 (3 6) | 5.2 (18 6) | † |
| 8 | RP | 3.3 (7.6) | 1.9 (4.3) | 2.3 (5 4) |
| 9* | RP | 4.0 | 5.0 | 6.9 |
| 10 | RP | 4.2 (14.3) | 4 4 (16.6) | † |
| 11 | RP | 2.0 (3.4) | 2 4 (5 6) | 3.0 (7.0) |
| 12 | RP | 3 4 (7.9) | 3 2 (7.7) | 6.2 (23.3) |
| 13‡ | Lingula | 2.8 | 6 0 | 6.0 |

*Initial CT scans performed elsewhere—area not available.
†Surgery performed soon after chemotherapy completed.
‡CXRs only available.
RP = retroperitoneum.

showed extensive cystic change. The macroscopic appearance varied, with some composed of relatively few thin walled cysts up to several centimetres in diameter, while others consisted of numerous smaller cysts within a solid stroma (Fig. 1).

Microscopically, the dominant tissue component in all metastases was teratoma differentiated with widespread cystic change. The cysts were mostly lined by a simple glandular epithelium, although squamous epithelium was also present in almost every tumour deposit. The stroma was predominantly fibromuscular. Cartilage was present in half of the cases. In 5 patients there was quite extensive tissue immaturity, particularly of stromal elements in which mitotic activity was usually apparent. In no case was there evidence of microscopic MTU, yolk sac tumour, malignant teratoma trophoblastic or seminoma. In 1 case there were microscopic foci of irregular mucus secreting glands apparently invading a fibrous stroma, interpreted as adenocarcinoma developing within teratoma differentiated, rather than MTU. No metastasis included extensive areas of necrosis or fibrosis, although this was a minor component in 4 cases.

### *Surgery*

Ten patients had resection of retroperitoneal masses, 2 had a combined thoraco-abdominal procedure for simultaneous resection of pulmonary and abdominal disease, and 1 patient had a hilar mass removed. The time between completion of chemotherapy and surgical removal of the residual masses varied from 1 to 25 months, although 8 of the 13 patients were operated on within 2 months of finishing chemotherapy. Patient no. 5 had surgery before his planned chemotherapy was completed, as outlined in the case history. Two of our patients (nos 8 and 11) had delays of 5 and 16 months before unequivocal enlargement of small retroperitoneal masses was documented. Long delays in definitive surgery occurred in 2 patients referred from other centres in whom the diagnosis of growing teratoma had not been recognised. The first of these (no. 9) had 2 laparotomies to explore and drain a presumed retroperitoneal "abscess" but biopsies revealed teratoma differentiated and total resection was not attempted. The second patient was deemed inoperable at a previous laparotomy at another centre.

Surgical resection of residual disease was complete in 11 cases. One of the patients with incomplete resection is alive and well with stable retrocrural disease 21 months following surgery, while the other has died following further surgery (see above case history). A further 10 patients are alive and well with no evidence of disease between 1 and 68 months (median 20) after surgery. The remaining patient relapsed 2 months later following a successful craniotomy and radiotherapy.

Retroperitoneal surgery was technically demanding in many of the 11 patients who had para-aortic masses removed. Four patients had disease adherent to the aorta or inferior vena cava (IVC), 1 had disease adherent to and displacing a ureter and in a further case, disease was attached to the duodenum which had to be opened to facilitate complete resection. Four patients sustained damage to major vessels during surgery: 2 to renal veins, 1 to a renal artery and 1 to the aorta requiring a replacement aortic graft. No nephrectomies were required.

One of our patients developed a gastrointestinal haemorrhage 6 months after surgery. The patient sustaining damage to the renal artery has controlled hypertension and has also required further surgery to free peritoneal adhesions.

Ten patients had normal tumour markers at the time of surgery and the remaining 3 had minor elevations of BHCG or AFP. In each case the tumour markers fell to normal shortly after surgery and remained normal without further treatment.

Three patients had 2 cycles of post-operative chemotherapy as histological reports at the time described microscopic tumour. On review, however, in only 1 patient (no. 5) was microscopic tumour found in the resected specimen and histology was typical of adenocarcinoma.

Twelve of the 13 patients are alive and well (10 are disease-free) with a median follow-up of 28 months.

## Discussion

Logothetis *et al.* (1982) described the growing teratoma syndrome as a distinct entity in their report of 6 patients. This and previous series (Tait *et al.*, 1984; Tonkin *et al.*, 1989) have documented the occurrence of this syndrome in between 1.9 and 3.3% of patients with metastatic teratoma treated with chemotherapy. Our data suggest that the syndrome is more common, with an incidence of 7.6%. We did include 1 patient with microscopic adenocarcinoma in the resected metastasis and whether other groups included such cases is unclear and may have affected the reported incidence.

The growing teratoma syndrome can manifest itself at a number of anatomical sites. Table 3 summarises the results and compares them with the published data. The retroperitoneum is the single most common site followed by the chest. Most patients had growing teratoma lesions at metastatic sites involved at presentation, but 1 of our patients (no. 13) developed a growing metastasis at a previously uninvolved site (lingula). However, this patient did not have CT scanning and was assessed by CXR only.

Growing teratoma lesions can become apparent during chemotherapy for metastatic disease, as occurred in most of our patients, or they may appear after a significant "disease-free" interval. Case no. 7 had an interval of 15 months following chemotherapy before his growing retroperitoneal lesion became manifest. In the series of Logothetis *et al.* (1982), 3 patients had disease-free intervals of 3, 4 and 5 months respectively.

Metastases may initially show a reduction in size during chemotherapy and begin enlarging later in the course of treatment (as in case no. 6) and this has been documented by other centres with initial reductions in tumour volume of up to 40% (Husband *et al.*, 1982). These patients may go unrecognised unless CT scans are repeated during chemotherapy and clinical suspicion of enlarging metastases should prompt radiological confirmation. Case no. 2 demonstrates that teratoma differentiated may grow at one site while remaining static at another.

The exact timing of surgery for enlarging residual masses depends on a number of factors. In general, no patient should be operated on until at least 4 cycles of cisplatin-containing chemotherapy have been delivered and ideally patients should have 2 cycles of chemotherapy after tumour markers have normalised. However, our data confirm that minor elevations of tumour markers at the completion of chemotherapy are compatible with the finding of residual teratoma differentiated (Dexeus *et al.*, 1989; Williams *et al.*, 1989).

Surgery can often be planned in advance if during treatment metastases are seen to enlarge in the face of normalising tumour markers. Patients in the present series usually had surgical resection of residual masses as soon as practicable after completion of chemotherapy; 8 patients had surgery within 2 months of completing chemotherapy. This is a shorter time than that reported by Logothetis *et al.* (1982) and Lorigan *et al.* (1988), who noted that growing retroperitoneal masses were followed up by CT scanning for 3 to 5 months before surgery. Our belief is that there should be no delay in surgery. Patients in whom surgery is delayed can

**Table 3** Reported Cases of Growing Teratoma Analysed by Anatomical Site

| *Authors* | *Total no. of cases* | *No. of sites* | *Anatomical site* | | | |
|---|---|---|---|---|---|---|
| | | | *Liver* | *Chest* | *Retroperitoneum* | *Nodes* |
| Hong *et al.* (1977) | 3 | 3 | – | – | 2 | 1 |
| Carr *et al.* (1981) | 2 | 4 | 1 | 1 | 1 | 1 |
| Logothetis *et al.* (1982) | 6 | 6 | – | 1 | 2 | – |
| Levitt *et al.* (1985) | 2 | 3 | – | 1 | 2 | – |
| Lorigan *et al.* (1988) | 5 | 6 | – | 1 | 5 | – |
| Tonkin *et al* (1989) | 8 | 10 | – | 2 | 7 | 1 |
| Jeffery (present study) | 13 | 15 | – | 3 | 12 | – |
| Total | 39 | 47 | 1 | 11 | 32 | 3 |

develop inoperable disease and locally advancing tumour may cause severe renal obstruction (Tait *et al.*, 1984; Levitt *et al.*, 1985; Lorigan *et al.*, 1988), biliary and duodenal obstruction (Levitt *et al.*, 1985) or death (Tait *et al.*, 1984; Loehrer *et al.*, 1986).

Surgery is often difficult and early exploration optimises the chances of a complete resection, which is necessary for long-term survival. Such aggressive surgery can be justified if long-term survival is achieved (Loehrer *et al.*, 1986), although other groups have reported surgery-related deaths (Hong *et al.*, 1977; Hendry *et al.*, 1980; Tait *et al.*, 1984; Tonkin *et al.*, 1989). Multiple operations have been necessary in some cases (Hong *et al.*, 1977; Loehrer *et al.*, 1986) and this has been necessary in one of our patients. Patients should be followed up closely since relapses with teratoma or carcinoma may occur in as many as 19% of patients (Loehrer *et al.*, 1988) and 1 of our patients has relapsed with MTI.

The administration of interferon has been reported to induce shrinkage of some metastases composed solely of teratoma differentiated (Rustin *et al.*, 1984; Tonkin *et al.*, 1989) but published experience with this agent is scarce. Some authors have advocated radiotherapy to residual retroperitoneal disease after chemotherapy (Read *et al.*, 1986). Whether such treatment has any role in the treatment of unresectable growing teratoma is unknown. Drainage of cystic masses has been used to palliate some patients with inoperable lesions (Tait *et al.*, 1984).

A noteworthy feature of the primary testicular tumours in this series is the prominence of yolk sac elements, especially in combination with immature elements of teratoma differentiated. Indeed, in 3 cases the only high grade tumour component was a yolk sac element. The metastases from all 3 of these patients included immature elements.

Although the continued enlargement of tumour deposits in some cases may be explained on the basis of fluid distension of the cysts, there can be little doubt from the morphological features of tissue immaturity with mitotic activity that some metastases were actively growing tumours.

A feature common to the reports of growing teratoma (and indeed the 13 patients in our series) is that all patients had received radiotherapy, chemotherapy or both and such treatment has been postulated as having an aetiological role in this syndrome (Hong *et al.*, 1977; Logothetis *et al.*, 1982; Lorigan *et al.*, 1988). However a few cases have been reported of patients with stage I teratoma treated with orchiectomy alone developing metastases of teratoma differentiated (Wogalter and Scofield, 1962; Kedia and Fraley, 1975; Kusuda *et al.*, 1986).

We believe the growing teratoma syndrome is more common than previously reported and all oncologists should be aware of the variety of sites and clinical settings in which it can occur. Such patients should be identified and operated on early, with complete surgical excision of all visible disease as the immediate goal. Close follow-up should then ensue to detect recurrences early, with further surgery being performed if necessary.

## Acknowledgement

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# Experience with Childhood Urolithiasis

## Report of 196 Cases

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Summary—A total of 196 children with urinary calculi were treated surgically. Their ages ranged from 1 to 14 years. The male:female ratio was 3:1. Stones were located in the kidney in 96 patients, in the bladder in 52 and in the ureters in 32. Multiple organ involvement was present in 16 patients and associated urinary tract anomalies were found in 11. Stone analysis revealed calcium oxalate and phosphate stones in 121 patients, struvite stones in 60 and uric acid stones in 15.

There are great differences in the extent of stone disease between the industrialised western countries on the one hand and the Middle East, Asia, Africa and South America on the other (Bennett and Colodny, 1973; Ghazali *et al.*, 1973; Sutor *et al.*, 1974; Sinno *et al.*, 1979; Churchill *et al.*, 1980; Ljunghall, 1987; Polinsky *et al.*, 1987). In Turkey, urolithiasis is still the most common paediatric urological problem (Remzi, 1980; Remzi *et al.*, 1981, 1984; Tellaloglu and Ander, 1984).

The following is a retrospective collective study of 196 children suffering from urolithiasis who were admitted to 2 paediatric surgery clinics in 2 different hospitals in Ankara, Turkey.

### Patients and Methods

From January 1982 to January 1989, 196 cases of paediatric urolithiasis were admitted to the SSK Ankara Hospital and the Gazi University Paediatric Surgery clinics. Urine analysis and culture and routine biochemical analysis were performed on all patients on admission. All had complete radiological studies of the urinary tract to localise the stone and determine the presence of associated anomalies. Age, sex, presenting symptoms, type of operative procedure and complications were noted in all cases.

### Results

There were 143 boys (73%) and 53 girls (27%) in the series, a ratio of 3:1. The patients ranged in age from 1 to 14 years (Table 1). A positive family history was found in 11 children (5.6%).

The most common symptoms were abdominal pain in 74 patients (37.7%), urinary tract infection (UTI) symptoms in 89 (45.4%), haematuria in 58 (29.6%), nausea and vomiting in 30 (15.3%), flank pain in 18 (9.2%) and failure to thrive in 12 (6.1%); 3 cases were detected incidentally.

Urine cultures were obtained by clean catch technique and those with colony counts of more than 100,000/ml were accepted as positive. At presentation, 69 patients (35.2%) had positive urine cultures, *Escherichia coli* and species of *Proteus* being the most commonly encountered microorganisms.

All patients had routine estimation of blood urea nitrogen, creatinine, calcium, phosphorus and uric

**Table 1** Age Distribution

| *Age (years)* | *No of patients (%)* |
|---|---|
| 1–5 | 90 (45.9) |
| 6–10 | 77 (39.3) |
| 11–14 | 29 (14.8) |
| Total | 196 (100.0) |

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acid. In 11 cases (5.6%) there were elevated serum creatinine levels. Similarly, in 8 patients (4.1%) serum calcium was found to be above normal limits. Uric acid tests revealed an increase in 6 cases (3.1%).

Stones were found in the kidney in 96 patients (49%), in the bladder in 52 (26.5%), in the ureters in 32 (16.3%) and multiple organ involvement was present in 16 cases (8.2%) (Table 2). The relationship between age and site of the stone is given in Table 3.

The urographic findings are listed in Table 4. Marked hydronephrosis was present in 48 patients (24.5%) and associated anomalies were found in 11 (5.6%): 21 radiologically non-functioning kidneys were confirmed by renal scintigraphy.

**Table 2** Location of Stones

| *Location* | *No of patients (%)* | |
|---|---|---|
| Kidney | | |
| Single | 70 (35.7) | (49) |
| Multiple | 22 (11.2) | |
| Staghorn | 4 (2.1) | |
| Bladder | 52 (26.5) | |
| Ureter | 32 (16.3) | |
| Multiple organ involvement | 16 (8.2) | |
| Total | 196 (100.0) | |

**Table 3** Location of Stones according to Age

| | *Age (years)* | | |
|---|---|---|---|
| *Location* | *1–5 (%)* | *6–10 (%)* | *11–14 (%)* |
| Kidney | 34 (37.8) | 45 (58.4) | 17 (58.6) |
| Ureter | 14 (15.6) | 11 (14.3) | 7 (24.1) |
| Bladder | 38 (42.2) | 11 (14.3) | 3 (10.3) |
| Multiple involvement | 4 (4.4) | 10 (13.0) | 2 (7.0) |
| Total | 90 (100.0) | 77 (100.0) | 29 (100.0) |

**Table 4** Urographic Findings

| | | *No of patients (%)* |
|---|---|---|
| Hydronephrosis | | |
| Minimal to moderate | | 42 (21.4) |
| Marked | | 48 (24.5) |
| Non-functioning kidney | | 21 (10.7) |
| Marked dilatation of involved ureter | | 16 (8.2) |
| Associated urinary anomalies | | |
| Pelviureteric obstruction | (2) | 11 (5.6) |
| Ectopic kidney | (3) | |
| Double collecting system | (2) | |
| Ureterovesical obstruction | (3) | |
| Unilateral renal agenesis | (1) | |

**Table 5** Operative Procedures

| *Procedure* | *No. of patients (%)* |
|---|---|
| Pyelolithotomy | 73 (33.5) |
| Nephrolithotomy | 18 (8.3) |
| Nephrectomy | 21 (9.6) |
| Cystolithotomy | 58 (26.6) |
| Ureterolithotomy | 41 (18.8) |
| Pyeloplasty | 2 (0.9) |
| Ureteroureterostomy | 2 (0.9) |
| Ureterovesico-neocystostomy | 3 (1.4) |
| Total | 218 (100.0) |

All patients required surgical intervention and 218 operative procedures were performed (Table 5). Open surgery was carried out as we do not have a paediatric extracorporeal shock wave lithotripsy (ESWL).

Stones were analysed biochemically. When the results of stone analysis were reviewed, calcium oxalate—phosphate stones were present in 121 cases (61.7%), struvite (magnesium ammonium phosphate) stones in 60 (30.6%) and uric acid stones in 15 (7.7%). Of the 138 children with upper tract stones, 40 (29%) were struvite, 96 (69.6%) were calcium oxalate-phosphorus and 2 (1.4%) were uric acid calculi; 25 bladder stones (43.1%) were calcium oxalate-phosphorus, 20 (34.5%) were struvite and 13 (22.4%) were uric acid calculi.

The overall complication rate was 4.1%. The most frequent complication was wound infection (2%) and this always occurred in flank incisions. Pelviureteric disruption occurred in 2 cases during pyelolithotomy (1%). Primary fishmouth pelviureteric anastomosis was performed in these cases, preserving the kidneys. Prolonged urinary discharge was encountered in 2 of the ureterolithotomies but they sealed off spontaneously.

## Discussion

Stones in the lower urinary tract are still common in some underdeveloped parts of the world: in these countries bladder stones are primarily a disease of children. In the industrialised part of the western world the incidence of bladder stones has continually decreased during the twentieth century and this disease is now rare. Parallel to this decrease, however, there is evidence of a marked increase in the formation of calcium-containing stones in the upper urinary tract (Ljunghall, 1987). This international variation in the type of calculi seen in children has long been noted. Studies from Europe usually report struvite calculi as the most common type (Ghazali *et al.*, 1973; Scholten *et al.*, 1973; Hodgkinson, 1977), while authors from the United States emphasise the higher incidence of metabolic stones (Paulson *et al.*, 1972; Bennett and Colodny, 1973; Malek and Kelalis, 1975). The presented series indicated that there had been a change in stone localisation in Turkish children. Approximately half of the patients had kidney stones while the other half was almost equally divided between bladder and ureteric stones. In the present study, calcium oxalate-phosphorus stones were present in 61.7% of patients and struvite stones in 30.6%. However, a different pattern of stone composition was noticed between the upper and lower urinary tract, indicating the higher incidence of calcium-containing stones in the upper urinary tract.

In all, 45.9% of our patients were in the 1- to 5-year age group. This correlates with other studies showing a decline in the incidence of urolithiasis after 5 years of age (Wenzle *et al.*, 1968; Troop *et al.*, 1972). In our series, this was more obvious in bladder stones, where the decline was sharper, from 42.2 to 10.3% (Table 3). Contrary to this finding, the incidence of upper tract stones was found to be increasing with age, from 37.8 to 58.6% for kidney stones and 15.6 to 24.1% for ureteric calculi. However, it is still true that there has been an overall decrease in the incidence of urolithiasis after pre-school age in Turkish children.

Although family history has been reported to be positive in over 50% of the children in endemic areas, it was positive in only 5.6% of the patients in our series (Paulson *et al.*, 1972; Sinno *et al.*, 1979).

The classical symptom of urolithiasis commonly encountered in adults (flank pain) was present in only 9.2% of our patients.

The reported incidence of UTI in relation to urolithiasis ranges from 9 to 76% (Paulson *et al.*, 1972; Sinno *et al.*, 1979). This was found to be 45.4% in our series, with *E. coli* and *Proteus* being the predominating micro-organisms.

The incidence of urinary tract anomalies associated with urolithiasis varies greatly in reports on paediatric urolithiasis. Developmental anomalies of the urinary tract were noted in 5.6% of patients who were predisposed to stone formation in addition to UTI.

According to Bennett and Colodny (1973), the incidence of nephrectomy for stone disease in children is 7%. In our series the rate was 9.6%.

Although extensive studies have been carried out in order to delineate the causes of stone formation, the underlying causes have not yet been found, other than some metabolic diseases and congenital urinary malformations. In this report too, no definite conclusions on the aetiology of the disease can be drawn.

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# Paediatric Urolithiasis in Greece

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Summary—A group of 44 patients, aged from 10 months to 14 years, underwent surgery for urinary calculi over a 7-year period (1982–1989). Eleven patients had bilateral or multiple calculi (total number of stones = 55, 20 of which were staghorn). Metabolic disorders (n = 25) and *Proteus* urinary infection (n = 15) were the 2 factors most often associated with lithiasis. Of the 55 stones, 51 were removed by open surgery. Complete stone clearance was achieved in 29 of 36 kidneys. Follow-up periods in the remaining 7 renal units (with small residual fragments) ranged from 3.5 to 7.5 years (mean 6.2) and revealed stone recurrence in only 2 patients. Evaluation of childhood urolithiasis should include thorough metabolic investigation and sound surgical judgment; effective management requires prolonged post-operative follow-up.

Urolithiasis is not an uncommon condition in children. Previous reports show an approximate incidence of 1–2/million total population of urinary stones amongst children less than 15 years of age in Western Europe and North America (Ghazali, 1975; Walther *et al.*, 1980). In the United States, the number of new patients with urolithiasis admitted to major paediatric institutions is estimated to be 5–10/year (Caldamone, 1983; Malek, 1985).

There are few reports concerning the long-term sequelae of childhood urolithiasis, and all are from North European or North American centres (Churchill *et al.*, 1980; Androulakakis *et al.*, 1982; Schoenenberger *et al.*, 1983).

Our 7-year experience of stones in children forms the basis of this report.

## Patients and Methods

Between 1982 and 1989, 52 children with urinary tract calculi were admitted to this department. Their ages ranged from 8 months to 14 years (median 4.2 years). All underwent radiological and metabolic evaluation according to our standard protocol (Tables 1 and 2). Eight children were lost to follow-up, following their discharge with instructions for conservative management. The remaining 44 patients, who were treated surgically, form the basis of this report. There were 32 boys and 12 girls,

**Table 1** Pre-operative Evaluation

- A Imaging
  - Plain KUB film
  - Intravenous urography
  - Micturating cystourethrography
  - Renal ultrasound
  - Tc-DMSA renal scan*
- B. Laboratory
  - Micturating specimen of urine
  - Urine culture
  - BUN and plasma creatinine
- C. Metabolic evaluation

*In patients with staghorn calculi only.

**Table 2** Metabolic Evaluation

- Blood and urine pH
- Plasma electrolytes
- Plasma Ca, P and alkaline phosphatase
- Blood uric acid
- Plasma PTH
- 24-h urine Ca determination
- 24-h urine P determination
- 24-h urine oxalate determination
- 24-h urine uric acid determination
- Urine aminoacids

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aged from 10 months to 14 years (median age, 4.5 years); 11 patients (25%) had bilateral or multiple calculi (total 55). The location of the stones is indicated in Table 3; only 2 patients had exclusively lower tract stones and both had purine metabolic disorders.

The presenting signs and symptoms are listed in Table 4; they were variable and no consistent clinical pattern could be identified, but macroscopic haematuria and recurrent abdominal pain were the most frequent manifestations.

Surgical management included a variety of procedures (Table 5). The stones removed were initially examined using straightforward, qualitative biochemical analyses but they were subsequently subjected to semi-quantitative infrared spectroscopy.

Follow-up ranged from 1 to 7.5 years (mean 5.8); however, 28 of the 44 patients (64%) had a post-operative follow-up of more than 3 years.

## Results

Metabolic disorders and chronic urinary infection were the 2 major factors associated with stone formation (Table 6). In only 5 patients (11%) were developmental genitourinary abnormalities found; these included vesicoureteric reflux of moderate degree in 2, pelviureteric junction stenosis in 1, horseshoe kidney in 1 and ureterocele in 1 patient.

**Table 3** Location of Calculi

| *Location* | *No. of patients* |
|---|---|
| Upper tract | |
| Kidney | 29 |
| Ureter | 2 |
| Kidney and ureter | 6 |
| Lower tract | |
| Bladder | 1 |
| Urethra | 1 |
| Both upper and lower tract | 5 |
| Total | 44 |

**Table 4** Clinical Signs and Symptoms

| *Sign or symptom* | *No of patients* |
|---|---|
| Macroscopic haematuria | 22 |
| Vague abdominal pain | 16 |
| Acute colic | 3 |
| Acute pyelonephritis | 3 |
| Chronic bacteriuria ($>10^5$/ml) | 15* |
| Dysuria (not associated with UTI) | 2 |
| Other | 2 |

**Proteus* was isolated in 13 cases.
Some patients had more than 1 symptom.

**Table 5** Operative Management

| *Operation* | *No of calculi* |
|---|---|
| Pyelolithotomy | 16 |
| Pyelocalicolithotomy | 10 |
| Pyelolithotomy + radial nephrotomies | 9 |
| Nephrolithotomy | 1 |
| Ureterolithotomy | 8 |
| Cystolithotomy | 6 |
| External urethrotomy and stone removal | 1 |
| Total | 51 |

In addition, 2 patients were treated by nephrectomy.

Only 2 renal units had to be removed because of irreparable damage. In both cases stone impaction into the ureter, complicated by ascending infection, had caused kidney destruction (calculus pyohydronephrosis).

Of the 36 kidneys operated upon with the aim of stone removal, 29 were rendered completely stone-free. In the remaining 7 renal units, small residual stones remained. Follow-up over periods ranging from 3.5 to 7.5 years (mean 6.2) showed stone recurrence in 2 cases. Four patients remained asymptomatic and in a stable condition; spontaneous passage of the residual fragment occurred in 1 case. Infrared spectroscopic analysis showed a mixed composition in 20 of 29 calculi. When grouped according to composition, infective and metabolic stones were found to be the most frequent (Table 7).

**Table 6** Pathogenic Factors

| *Pathogenic factor* | *No. of patients* |
|---|---|
| Metabolic disorders | 25 |
| Renal hypercalciuria | 10 |
| Absorptive hypercalciuria | 5 |
| Cystinuria | 4 |
| Hyperoxaluria | 4 |
| Renal tubular acidosis | 2 |
| Infection | 15 |
| *Proteus* | 13 |
| Genitourinary developmental anomaly | 5 |
| Unknown | 2 |

Table 7 Composition of 29 Calculi Submitted to Infrared Spectroscopic Analysis

| *Composition* | *No of calculi* |
|---|---|
| Calcium oxalate 100% | 2 |
| Calcium oxalate 80%+<br>Calcium phosphate 20% | 6 |
| Calcium phosphate 100% | 1 |
| Calcium phosphate 60%+struvite 40% | 13 |
| Calcium oxalate 80%+matrix 20% | 1 |
| Uric acid 100% | 1 |
| Xanthine 100% | 1 |
| Cystine 100% | 4 |
| Total | 29 |

## Discussion

In contrast to adult patients, the management of childhood urolithiasis has received scant attention. This may be due to the fact that many children with urinary stones have not been referred to paediatric centres which collate such data (Walther *et al.*, 1980). Paediatric patients with urinary calculi must be treated in paediatric urological units which can provide long-term surveillance and accurate follow-up data, if valid conclusions from large series of patients are to be drawn in the future.

The data presented in this study indicate that metabolic disorders, followed by chronic urinary infection caused by *Proteus* strains, constituted the main factors associated with stone formation. This high incidence of metabolic disorders may reflect the consistency with which metabolic assessment was performed in each case. It was found that children in this south-eastern corner of the European continent follow a similar pattern regarding the pathogenesis of urolithiasis to that of their North European and North American counterparts (Churchill *et al.*, Walther *et al.*, 1980; Schoenenberger *et al.*, 1983).

Twenty of the 55 stones (36%) were staghorn. This constitutes an impressive series of staghorn calculi in children and will form the subject of a separate report. It must be noted, however, that 13 of the 20 staghorn calculi analysed by infrared spectroscopy contained struvite in significant quantities (up to 40%).

It should also be noted that 10 of the 11 patients with bilateral or multiple stones had an underlying metabolic disorder; 5 primary hypercalciuria (3 of the renal and 2 of the absorptive type), 3 cystinuria, 1 hyperoxaluria and 1 hyperuricosuria. Conversely, 10 of the 25 patients (40%) with identifiable metabolic disorders had bilateral or multiple stones. The presence of bilateral or multiple stones in children should therefore arouse strong suspicion of a possible metabolic disorder.

In children with renal calculi, every effort should be made to preserve the affected kidney. The 4.7% nephrectomy rate in this series seems acceptable. In 36 kidneys, stone removal was achieved by open surgery alone without the aid of extracorporeal or percutaneous lithotripsy; 29 kidneys were rendered stone-free. Incomplete stone clearance in the remaining 7 kidneys was associated with the presence of small caliceal fragments in addition to a staghorn calculus. These patients were closely observed post-operatively and received appropriate medical treatment. Patients with renal hypercalciuria received oral thiazides, 0.5–1 mg/kg/day; children with absorptive hypercalciuria were put on a low calcium diet and those with infected stones were kept under long-term chemoprophylaxis with co-trimoxazole. All were instructed to maintain a high urine output of >2 l/24 h.

It may be argued that the percentage of renal units incompletely cleared of stone at operation (19%) was relatively high, especially in view of the patients' young age. It must be noted, however, that all residual stones were very small caliceal fragments. It has been the experience of other authors that such small residual fragments in children do not necessarily cause either symptoms or stone recurrence (Vahlensieck, 1968; Borgmann and Nagel, 1980; Androulakakis *et al.*, 1982) and long-term follow-up in our patients has confirmed this. Only 2 of the 7 patients had a recurrence. Both had primary hypercalciuria and suffered from recurrent bacteriuria during the post-operative period. This "hands-off" policy might change, however, in the near future, as ESWL treatment gradually becomes accepted in the management of urinary stones in children. If, therefore, after an initial period of observation, spontaneous passage of residual fragments seems unlikely, ESWL may be contemplated.

In summary, the evidence from this study confirms that childhood urolithiasis in Greece is closely associated with metabolic disorders, hypercalciuria being most frequently encountered. Infective stones, however, represent the single most common type observed. Open surgery can be regarded as effective and safe, but prolonged post-operative follow-up is essential, especially in patients with residual fragments.

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# Detrusor Hyper-reflexia as a Factor in Spontaneous Perforation of Augmentation Cystoplasty for Neuropathic Bladder

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Summary—In a series of 30 children undergoing cystoplasty for neuropathic bladder, 14 had a combination of a competent sphincteric mechanism and detrusor hyper-reflexia. All 3 cases of spontaneous perforation of the augmentation occurred within this latter group and it is postulated that excessive intravesical pressure due to high pressure hyper-reflexia was the causal factor. Strategies to reduce the risk of perforation are discussed.

As enterocystoplasty, in one form or another, is used increasingly in the management of patients with neuropathic bladder, so also do its complications increase. Among the more serious of these is spontaneous perforation and our experience suggests that patients with a combination of high pressure detrusor hyper-reflexia and a competent sphincteric mechanism are especially at risk.

## Patients and Methods

Between 1984 and 1989 we performed augmentation cystoplasty in 30 children with neuropathic bladder. There were 23 girls and 7 boys and their ages ranged from 2 to 16 years (mean 10). All but 5 (2 lumbosacral lipoma, 2 sacral agenesis, 1 spinal cord trauma) had myelomeningocele. With the exception of 1 patient, a pouched, detubularised augmentation was constructed (Williams *et al.*, 1988) using sigmoid colon (27), ileum (2) or ileocaecum (1). Video-urodynamic assessments were conducted as previously described (Rickwood *et al.*, 1982).

## Results

Indications for cystoplasty fell into 3 categories.

Fourteen patients had marked genuine stress incontinence (GSI) requiring surgical correction, combined with detrusor non-compliance (end-filling pressure (EFP) > 20 cm $H_2O$ at physiological capacity) (10 patients) and/or detrusor hyper-reflexia (8). Maximum pressures generated by detrusor contractions never exceeded 30 cm $H_2O$. GSI was treated in 1 boy by AMS urinary sphincter and in 13 girls by Marshall-Marchetti bladder neck suspension with post-operative voiding by clean intermittent self-catheterisation (CISC). In 2 girls the results were unsatisfactory because of persistent GSI. In the remainder, who are continent, urodynamic assessment showed bladder capacity to be determined by contractions of the intestinal segment. Pressures generated were modest, never exceeding 30 cm $H_2O$, but more than sufficient to overcome sphincteric resistance. No spontaneous perforation occurred during follow-up ranging from 6 to 63 months (mean 28).

Two patients had useful urethral resistance combined with detrusor non-compliance, so that GSI developed as the bladder filled. Both are dry post-operatively on CISC and during follow-up periods of 44 and 7 months, neither has developed spontaneous perforation.

Fourteen patients had a fully competent sphincteric mechanism, with a bladder capacity compromised solely by detrusor hyper-reflexia unresponsive to oxybutynin or propantheline. Maximum pressures generated by detrusor contractions

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were <20 cm $H_2O$ (1 patient), 20 to 60 cm $H_2O$ (7) and >60 cm $H_2O$ (6). Six patients had detrusor non-compliance as already defined. During follow-up periods ranging from 5 to 65 months (mean 24), 3 patients suffered spontaneous perforation of their augmentation.

## Case Reports

*Case 1.* Female, myelomeningocele, D12 complete. CISC alone was unsatisfactory and although addition of oxybutynin achieved continence, side effects forced its abandonment. Propantheline was ineffective. Video-urodynamic study showed no GSI; capacity was 100 ml (EFP <10 cm $H_2O$) and maximum detrusor contraction pressures were 80 cm $H_2O$ in association with detrusor-sphincter dyssynergia. A sigmoid pouch cystoplasty was performed at 15 years of age and she became continent on 4-hourly CISC plus propantheline. Perforation occurred 4 months post-operatively in the early hours of the morning. The evening before she had attended a social function, had drunk more than usual and had not catheterised on returning home. Laparotomy showed a perforation at the apex of the augmentation anteriorly. Subsequent progress (20 months) was uneventful and she is dry on regular CISC without medication.

*Case 2.* Male, myelomeningocele, L3 complete. CISC alone was ineffective and only slight improvement occurred with oxybutynin and propantheline. Urodynamic findings were similar to those in Case 1: capacity was 180 ml (EFP<10 cm $H_2O$) and maximum detrusor contraction pressures exceeded 100 cm $H_2O$. Sigmoid pouch cystoplasty was performed when he was 12 years of age and gave full continence on 4-hourly CISC plus propantheline. Perforation occurred 3 months post-operatively, again in the early morning. He was attending a Scout camp at the time and had been catheterising irregularly. At laparotomy, the perforation was sited as in case 1. Subsequent progress (21 months) has been satisfactory on a regime of CISC plus oxybutynin.

*Case 3.* Female, spinal cord trauma, D4 complete. Marked left vesicoureteric reflux developed 6 years after her injury. This resolved on CISC but she remained incontinent despite the addition of oxybutynin and propantheline. Urodynamic findings were as in case 1; capacity was 10 ml (EFP<10 cm $H_2O$) and maximum detrusor contraction pressures exceeded 100 cm $H_2O$ Augmentation cystoplasty, with a sigmoid pouch, was performed when she was 11 years old. At that time, perforation had already occurred in cases 1 and 2 and was thought to have resulted solely from over-distension. Accordingly, a regime of strict 4-hourly CISC (plus propantheline) was advised and duly observed. Continence was perfect but perforation occurred 5 months post-operatively. Because of her high neurological level, symptoms were diffuse and caused a delay in admission to a distant hospital where inexperience led to further delay in diagnosis. Despite ultimate laparotomy, she died some 30 h after the onset of symptoms. The site of perforation was the same as in cases 1 and 2.

## Discussion

Although the site and early timing of perforation in all 3 patients were similar, others have described this complication occurring at various sites, including suture lines, and 2 years or more post-operatively. This also includes reports of re-perforation (Elder *et al.*, 1988; Sheiner and Kaplan, 1988; Webber *et al.*, 1989). Various causes have been suggested. Direct damage by metal catheters is possible but unlikely when, as in our patients, flexible catheters were used. Other suggestions have included transmural infection and local ischaemia caused by adhesions.

Simple over-distension, due to delayed or inadequate CISC, seems a more plausible explanation and was probably contributory in Cases 1 and 2. Nevertheless, in some circumstances, marked over-distension is improbable and high pressure over-distension even less likely. In the presence of marked GSI, high pressure hyper-reflexia is impossible even when the detrusor is capable of mounting strong contractions. Our experience with these and other patients is that when GSI is corrected, by artificial sphincter or by bladder neck suspension, modest rises in the intrinsic intravesical pressure (approximately 30 cm $H_2O$) are sufficient to overcome outlet resistance regardless of whether such pressures derive from contractions of either the detrusor or the intestinal segment. In the absence of either of these, a rise in baseline intravesical pressure may suffice. This applies to patients in our first 2 categories; even if CISC were abandoned altogether, the likely result would be no more than moderate over-distension at modest intravesical pressure. Spontaneous perforation might not be expected and, indeed, has not occurred so far.

The situation for patients in the third category who have a urodynamic picture typical of supra-sacral cord lesions (Thomas, 1976) is very different. The sphincteric mechanism is proof against rises in intra-abdominal pressure and comparatively high pressure detrusor contractions are required to overcome detrusor-sphincter dyssynergia. Following augmentation cystoplasty, such contractions would tend to distend the augmentation rather than result in voiding, and we suggest this as a cause of perforation, especially if combined with a degree of over-distension. It may be significant that the complication occurred in none of the 8 patients with maximum detrusor pressures under 60 cm $H_2O$ but in 3 of the 6 patients with pressures exceeding this level.

If our hypothesis is correct, what can be done to reduce the risk? Regular and efficient CISC is clearly desirable but, as case 3 illustrates, not guaranteed to be effective. Medication to inhibit detrusor contractions might help. Propantheline was given in these 3 patients in the almost certainly mistaken belief that contractions of the bowel segment, rather than the detrusor, would be the major factor limiting bladder capacity post-operatively. A more potent detrusor antispasmodic, such as oxybutynin (if tolerated), might be more effective. Neurological ablative procedures, to minimise or abolish detrusor contractility, have drawbacks. It would appear that sub-trigonal phenolisation is effective only in the short term. Sacral rhizotomy is difficult (or impossible) in myelomeningocele patients, whilst in other situations the complete bilateral rhizotomy necessary to secure a permanent effect also runs the risk of exchanging hyper-reflexia for a combination of GSI and detrusor non-compliance. Other forms of cystoplasty could be considered. Reported complications relate almost exclusively to pouched augmentations and the clam cystoplasty (Bramble, 1982) may not involve this complication. Substitution cystoplasty would eliminate the problem of hyper-reflexia, but not that of high sphincteric resistance, so that extreme overdistension leading to perforation is still theoretically possible. Finally, because the bladder neck is usually competent in patients at risk, sphincterotomy could be performed to reduce detrusor-sphincter dyssynergia and hence also reduce maximum detrusor contraction pressures.

## Postscript

Since submission of this article we have been made aware of 2 cases of spontaneous perforation following ileal clam cystoplasty (Bramble, 1982).

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# Case Reports

## Hepatocellular Carcinoma and Treatment with Cyproterone Acetate

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### Case Report

A 75-year-old man presented with outflow tract obstruction and was found to have a TOb well differentiated carcinoma of the prostate following transurethral resection of his prostate. Serum acid phosphatase (SAP) was elevated at 5.6 iu/l (normal 0–2 iu/l) but liver function tests, creatinine and bone scan were within normal limits. He was commenced on cyproterone acetate 100 mg 3 times a day. He remained well for 18 months, when he presented with orthopnoea. Physical examination revealed bilateral crepitations and also the presence of 4 finger smooth hepatomegaly. Chest X-ray showed changes consistent with fibrosing alveolitis but no evidence of metastatic disease. SAP was normal (0.9 iu/l). Liver function tests were abnormal, aspartate transaminase 35 iu/l (0–24) bilirubin 43 mol/l (0–17), alkaline phosphatase 240 iu/l (70–210). Ultrasound examination revealed the presence of a 6.5 cm rounded lesion in the left lobe of the liver. A needle biopsy was performed and histological examination confirmed the presence of hepatocellular carcinoma. Serum carcinoembryonic antigen levels and alphafetoprotein levels were normal and he was hepatitis B surface antigen negative. His cyproterone acetate was discontinued and no further treatment was given in view of his age and clinical condition.

### Comment

The reported incidence of hepatic side effects is low with cyproterone acetate (CPA). Since 1974 there have been 17 reports of hepatic dysfunction during CPA administration, only 2 of which were reported to the Committee on Safety of Medicines (CSM). Cholestatic jaundice has been most commonly reported, which resolves on withdrawal of drug therapy. This is the first reported case of hepatocellular carcinoma in a patient on CPA treatment.

Although CPA is used as an anti-androgen in the treatment of prostatic carcinoma, because of its steroid structure it also has a progestogen action. The progestogens have been shown to cause liver adenomas in rats at doses 50–150 × the dose found in the oral contraceptive pill (CSM, 1972). CPA has been shown to cause the development of liver adenomas in rats at 1250 × the progestogen dose-equivalent found in the oral contraceptive (Schuppler and Günzel, 1976). CPA stimulates only hyperplasia at lower doses, although other chemical inducers of liver growth stimulate both hyperplasia and liver hypertrophy. CPA induces rises in the level of liver mono-oxygenases and a dose-dependent increase in liver weight in rats. In models of hepatocarcinogenesis, it causes increases in DNA synthesis and mitoses within 24 h of administration. The state of the exposed liver is also of importance. A recent study, comparing the proliferative effects of CPA on livers of 3-week-old adult rats and partially hepatectomised adult rats, found the greatest increase in liver weight in previously hepatectomised animals, where the normal growth-restraining mechanisms may be absent. CPA withdrawal resulted in subsequent apoptosis of liver cells and reduction in liver mass towards normal levels (Alison *et al.*, 1987).

A cause and effect relationship is difficult to prove in this case, but in view of the known proliferative action of CPA in animal models, it may act as a promoter of hepatocarcinogenesis in man, or contribute to the rate of growth of a pre-existing hepatic tumour. All patients receiving CPA therapy warrant regular assessment for hepatic dysfunction and all hepato-toxicity needs to be reported to the CSM.

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# Penile Metastases from Basaloid Carcinoma of the Anal Canal

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## Case Report

A.A., a 40-year-old male, presented in February 1986 with a 2-month history of bleeding *per rectum* and pain during and after defaecation. On physical examination the only abnormality was an ulcerated growth 3 cm above the anal verge. Biopsy confirmed the diagnosis of basaloid carcinoma of the anal canal (Fig. 1). Serum chemistry, haemogram, chest X-ray and ultrasound scans of the abdomen and liver were normal. A synchronous combined abdominoperineal resection was performed in February 1986. The resected specimen showed that the ulcer was mostly confined to the mucosa and submucosa involving superficial muscle layers only. Abdominal lymph nodes did not show any secondary deposits.

In May 1987 he complained of difficulty in passing urine. The urinary flow rate was consistent with bladder neck obstruction. Bladder neck incisions were made at 5 and 7 o'clock to relieve the obstruction and he was followed up regularly. In December 1988 he was admitted with acute retention of urine. Physical examination was unremarkable except for 2 hard masses (2.5 × 1.5 and 1 × 0.5 cm) at the subcoronal and penoscrotal junction of the shaft of the penis respectively. Suprapubic percutaneous cystostomy was performed as urethral catheterisation was not possible.

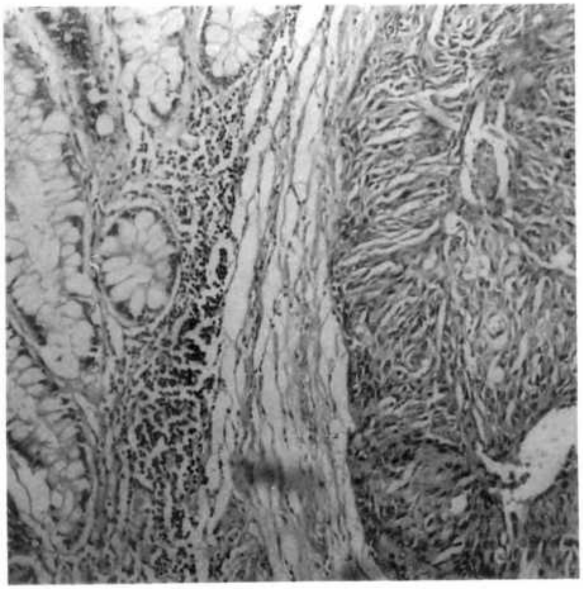

**Fig. 1** Basaloid carcinoma of anal canal. Adjacent normal mucosa is also seen. (H and E × 100).

Fine needle aspiration cytology from the penile mass revealed tumour cell deposits of basaloid cell type. Total penectomy with perineal urethrostomy was performed in December 1988, after a complete blood count, serum chemistry, chest X-ray and ultrasound scans of the abdomen, liver and bone were found to be normal. Histopathology of the penile lesions confirmed the metastatic nature of the secondaries from a basaloid carcinoma (Fig. 2).

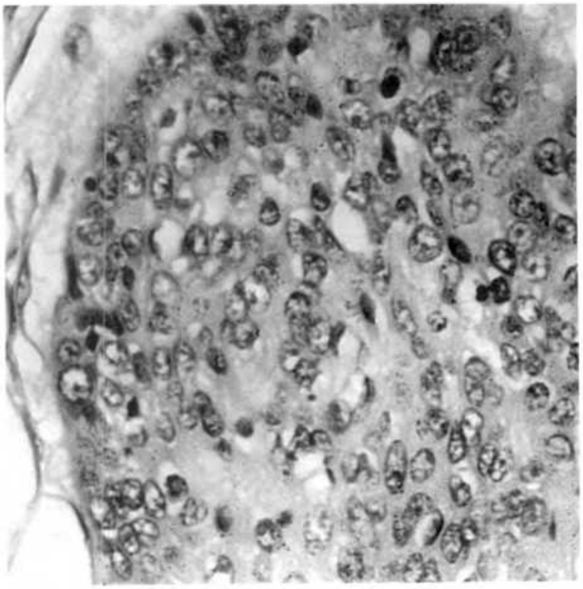

**Fig. 2** Metastatic tumour deposits of basaloid type of carcinoma in penis. (H and E × 400).

## Comment

Penile metastases, although rare, present a challenging problem. Treatment has included surgery, chemotherapy and radiotherapy (alone or in combination) (Robey and Schellhammer, 1984; Powell *et al.*, 1985). The prognosis is poor and most patients die within a year. Occasional survivals of 5 to 9 years after surgical excision have been reported (Haddad and Manne, 1987), suggesting that radical surgery might be effective, particularly in patients with a rectosigmoid primary. Acute retention of urine is less common because urethral involvement is unusual (Robey and Schellhammer, 1984). In contrast, our patient presented with acute retention due to complete urethral involvement by the secondaries.

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# Carcinoma of the Urachus Associated with Urachal Adenoma

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## Case Report

A 54-year-old lady presented with blood and mucus in the urine. Initial cystoscopy showed a fronded tumour at the bladder apex and transurethral resection was performed. Histology showed adenocarcinoma. On the second follow-up cystoscopy 5 months later, there was a recurrence at the same site but with intact overlying epithelium; bimanually, it was a 4-cm mobile tumour. Laparotomy confirmed an encapsulated tumour on the vault of the bladder attached to the urachus (Fig. 1). *En bloc* excision of the urachal mass and partial cystectomy were performed.

Histology of this lesion revealed dysplastic areas that represented a pre-existing adenoma and also areas showing a frankly invasive, poorly differentiated adenocarcinoma (Fig. 2).

## Comment

Malignant urachal lesions are rare and the majority are adenocarcinomas (69% mucin-producing, 15% non-producing); the remaining 16% include sarcomas, transitional cells carcinomas and squamous cell carcinomas (Sheldon *et al.*, 1984).

The most common presenting complaint is haematuria and there is often a palpable suprapubic mass. About 25% of patients have mucus in the urine and this can be a valuable sign (Sheldon *et al.*, 1984). Intravenous urography may show distortion or a filling defect at the bladder dome. Ultrasound and CT scanning are both useful in assessing the size of a lesion (Fitzgerald and Pirani, 1985).

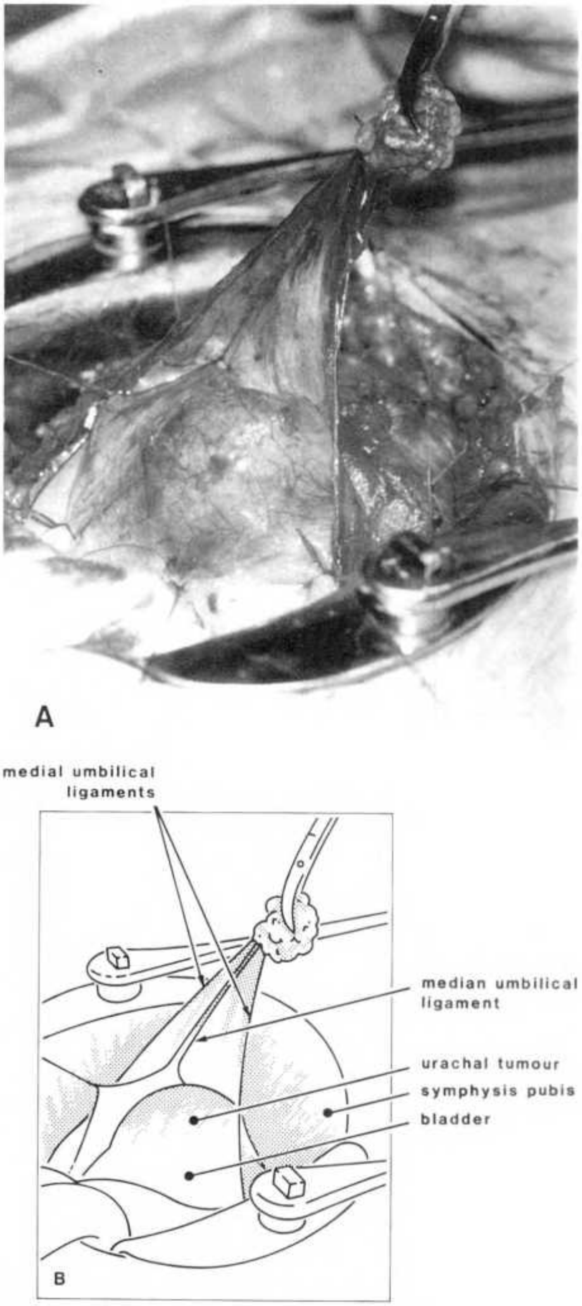

**Fig. 1A and B** The urachal tumour at laparotomy

Treatment is operative and radiotherapy is generally unhelpful. Chemotherapy has hitherto not been used in these patients (Curran *et al.*, 1987). The prognosis is poor, with an overall 5-year survival rate of 9%.

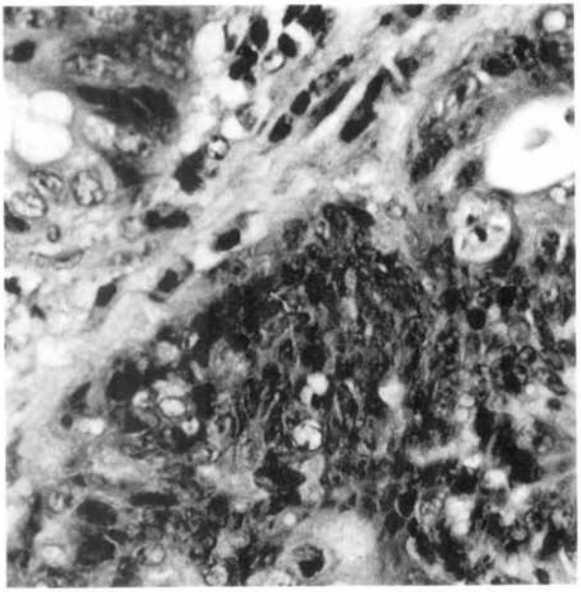

**Fig. 2** Invasive adenocarcinoma (H and E ×400)

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# Arteriovenous Malformation of the Spermatic Cord

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A hard, irregular scrotal mass is an indication for surgical intervention because of malignancy. These masses include germ cell tumours, paratesticular tumours, fibromas and chronic epididymitis. We present the second reported case of an arteriovenous malformation of the spermatic cord presenting as a hard scrotal mass. The first case was reported by Guz *et al.* (1989).

## Case Report

A 27-year-old man presented with a 4-week history of an asymptomatic scrotal mass. There was no history of trauma or infection. The mass was separate from his testes and did not transilluminate.

Scrotal exploration revealed a mass containing blood-like fluid (Fig.) but it did not appear malignant. The testis and epididymis were normal. The mass was excised and histological examination revealed arteriovenous malformation.

This benign lesion should be included in the differential diagnosis of paratesticular masses.

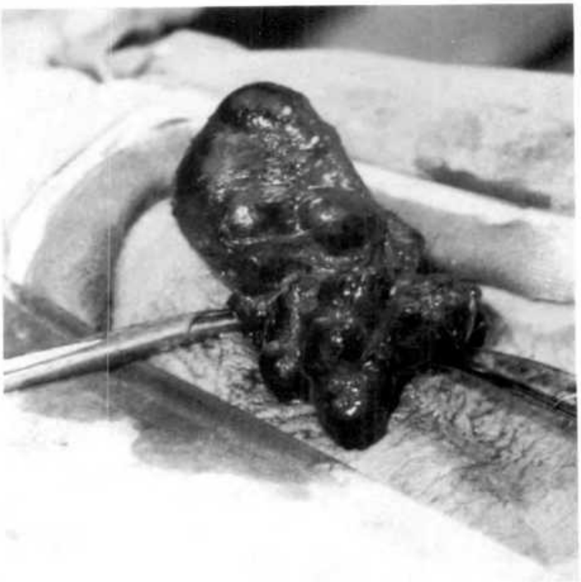

**Fig.**

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# Tumour-to-tumour Metastasis: Bladder Carcinoma Metastasising to an Adrenocortical Adenoma

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## Case Report

An 81-year-old woman was admitted to hospital for investigation of recent confusion. Examination revealed a disorientated woman without localising physical signs. She was hypercalcaemic (3.28 mmol/l) and in chronic renal failure (urea 15.8 mmol/l; creatinine clearance 26 ml/min). Intravenous urography showed a non-functioning left kidney. A urinary infection (*Proteus mirabilis*) was treated with antibiotics. Mithramycin was given intravenously to lower the serum calcium. Her general condition deteriorated gradually until death 25 days after admission.

At autopsy there was dilatation of the bladder with ulceration and thickening of the left lateral wall. The left ureteric orifice was obstructed by irregular firm white tumour, 3.5 cm in maximum diameter, with resultant hydroureter and hydronephrosis. A well circumscribed yellow nodule 1.5 cm in diameter was present in the right adrenal gland. Metastatic tumour was found in abdominal lymph nodes, liver, pleura and heart.

Histological examination showed a poorly differentiated transitional cell carcinoma. The adrenal cortex contained an encapsulated tumour composed of large clear cells within which discrete clusters of malignant cells were present, identical to the primary bladder carcinoma (Fig.).

## Comment

Bladder carcinoma is responsible for 3% of deaths from malignant disease, metastasising late in its course to lymph nodes, lung, liver and bone and in 5 to 12% of cases to adrenal glands (Fetter *et al.*, 1959). Adrenocortical adenomas are found in 2% of all autopsies. They are rarely identified as recipient tumours for metastatic carcinomas and were initially reported by Ortega *et al.* (1951) as a site for deposition of bronchogenic carcinoma. Most of the subsequent reports of donor neoplasms to adrenal adenomas have been of lung cancers but breast, kidney, colon, stomach and thyroid primaries have also been described (Scierski and Podworski, 1973). This is believed to be the first case of bladder carcinoma metastatic to an adrenocortical adenoma and, indeed, the first time that bladder carcinoma has been recognised as a component of a neoplasm-to-neoplasm metastasis, either as donor or recipient.

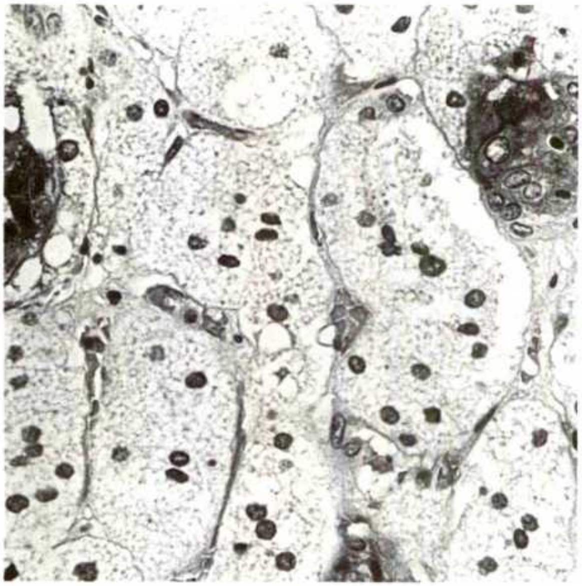

**Fig** Adrenocortical adenoma, containing large clear cells, within which 2 nests of pleomorphic metastatic bladder carcinoma cells can be seen. (H & E × 320).

## Acknowledgements

I thank Dr J. T. Leeming for permission to present clinical details of his patient and Dr E. W. Benbow for helpful discussion on the histopathology of this case.

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# Small Cell Carcinoma of the Prostate: Implications for Management

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A patient with known adenocarcinoma of the prostate presented 5 years after his initial diagnosis with liver metastases and Cushing's syndrome due to ectopic adrenocorticotrophic hormone (ACTH). He was treated with high dose aminoglutethimide and chemotherapy but died 2 months later after an initial response. Autopsy confirmed a small cell component within the liver and bone. There is evidence that chemotherapy is effective in these patients and should be considered as the treatment of first choice.

## Case Report

A 56-year-old white male presented with a 2-week history of malaise, weakness, facial and ankle oedema, polydipsia and polyuria.

Five years earlier moderately differentiated adenocarcinoma of the prostate had been diagnosed at transurethral resection. As it involved only the prostate the patient went on to receive radiotherapy. One year later he developed bony metastases and was treated initially by orchidectomy and then with flutamide. Recurrent bony pain necessitated hypophysectomy and subsequent glucocorticoid replacement therapy. Over the past 9 months he had received intravenous APD (3-amino-1-hydroxypropylidene-1,1-bisphosphonate) for persistent bony pain.

On examination he was noted to have Cushingoid facies, hepatomegaly, proximal muscle weakness and bilateral ankle oedema. He was normotensive and not pigmented.

Initial investigations revealed a hypokalaemic alkalosis with a serum potassium of 2.2 mmol/l and a bicarbonate of 34 mmol/l. A random blood glucose was 17 mmol/l. Serum sodium, urea and creatinine were within normal limits. Serum acid phosphatase was normal but the serum prostatic specific antigen was $>100$ µg/l (normal $<5$ µg/l). A 9.00 am cortisol was markedly elevated at $>2000$ nmol/l (normal $<700$ nmol/l) and did not suppress after a high dose dexamethasone suppression test (4 mg *qds* for 48 h). Serum ACTH was 282 ng/l (normal 10–80 ng/l).

Liver function tests were abnormal and an abdominal CT scan revealed extensive hepatic metastases in addition to bilateral adrenal enlargement. The chest X-ray was normal.

A diagnosis of ectopic ACTH production due to progressive prostatic carcinoma was made and treatment with aminoglutethimide 1250 mg daily was started. His metastatic disease was treated with Adriamycin and cyclophosphamide. Initially his condition improved and his serum cortisols returned to normal. However, over the next few weeks he became hyperpigmented, his weakness returned and his serum cortisol levels became elevated again. Two months later he died.

Autopsy showed bronchopneumonia and multiple metastases in liver and bone. A primary bronchogenic tumour was not identified and the lungs were free of metastases. Microscopically, the liver showed infiltration by a small cell tumour characteristic of "oat cell carcinoma type" (WHO, 1982) (Fig. 1). The vertebral bodies showed infiltration by adenocarcinoma, together with occasional intermingled foci of small cell tumour (Fig. 2). Immunohistochemistry showed positive staining for prostatic acid phosphatase (PAP) and prostatic specific antigen (PSA) within the adenocarcinomatous element while the small cell tumour showed no staining. The latter was also negative for the neuroendocrine markers neurone-specific enolase, chromogranin and PGP 9.5. Argyrophil granules were absent (Grimelius method).

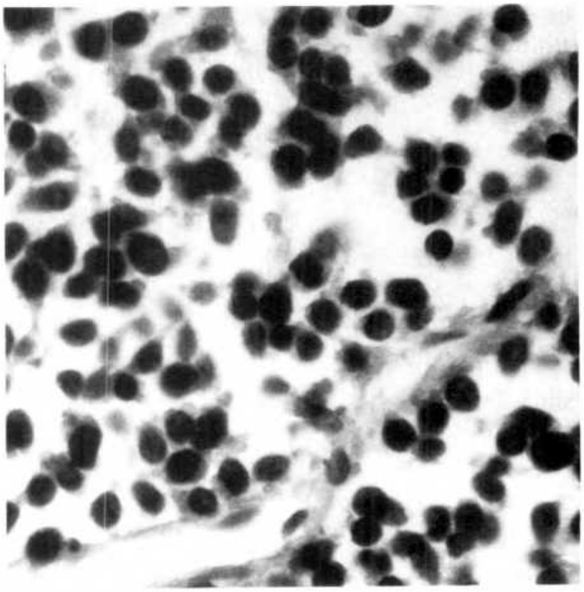

**Fig. 1** Liver showing infiltration by small cell carcinoma. (H and E × 500).

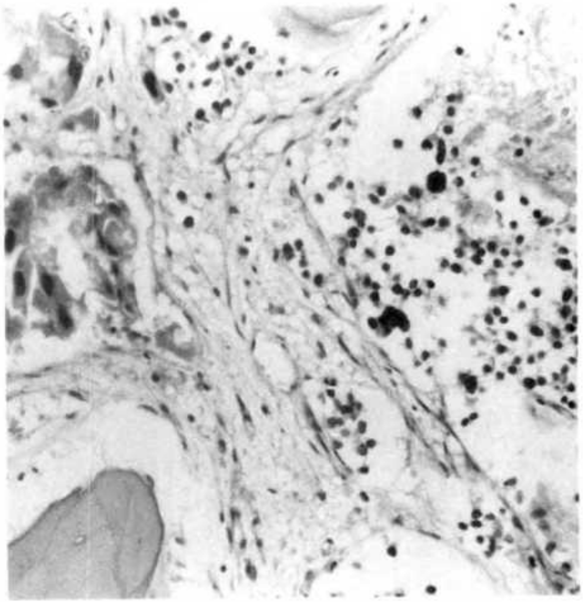

**Fig. 2** Bone with metastatic adenocarcinoma (left of figure) with adjacent small cell component. (H and E × 250).

## Comment

Prostatic carcinoma is seldom associated with biochemical or clinical abnormalities consistent with ectopic ACTH production. To date only 12 cases have been described and all have been associated with small cell undifferentiated or carcinoid variants of prostatic carcinoma (Jelbart *et al.*, 1988). However, only 50% of the patients with small cell undifferentiated carcinoma of the prostate (SCUCP) were associated with syndromes suggestive of ectopic ACTH.

SCUCP has been reported to occur in 1 to 10% of prostatic carcinomas (Jelbart *et al.*, 1988; Turbatt-Herrera *et al.*, 1988) and closely resembles the morphological pattern seen in bronchogenic small cell undifferentiated carcinoma. However, not all of these tumours stain positively for the neuroendocrine markers (Ro *et al.*, 1987).

The initial presentation of SCUCP may be similar to that of prostatic adenocarcinoma. Unlike prostatic adenocarcinoma, it tends to metastasise early to liver, spleen and lung and to unusual sites such as omentum, vocal cord, axillary lymph nodes and periadrenal soft tissue (Tetu *et al.*, 1987; Jelbart *et al.*, 1988). In patients with this variant the clinical course has been aggressive, with a reported median survival of only 5 months (Tetu *et al.*, 1987). SCUCP tends to respond well to chemotherapy (Hindson *et al.*, 1985; Tetu *et al.*, 1987) and therefore its recognition as a histopathological entity is of considerable importance.

This condition is almost certainly underdiagnosed and in patients with rapidly progressive disease, or biochemical abnormalities consistent with hormone secretion, the possibility of SCUCP should be considered even if recent biopsies show adenocarcinoma only.

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Requests for reprints to: I. E. Smith, Department of Medicine, Royal Marsden Hospital, Fulham Road, London SW3 6JJ.

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# Spontaneous Rupture of Hydronephrotic Kidney during Pregnancy

D. A. R. EL HALABI, M. S. HUMAYUN and J. M. SHARHA'AN, *Departments of Surgery and Obstetrics and Gynaecology, Al Adan Hospital, Kuwait*

Rupture of the urinary tract during pregnancy is uncommon. Pyelonephritis, painful overdistension and rupture are occasional effects of pregnancy on the urinary tract. We present a case of spontaneous rupture of a hydronephrotic kidney in a pregnant woman.

## Case Report

A 30-year-old Kuwaiti woman, mother of 8 children, was admitted to the Maternity Department on 5 December 1988 complaining of right flank pain, frequency of micturition and dysuria. Her general condition was satisfactory and she was 28 weeks pregnant. Examination revealed a tender mass in the right lumbar region and hypochondrium. Ultrasound showed hydronephrosis of the right kidney and a normal left kidney.

Urine culture revealed *Escherichia coli* and appropriate antibiotics were given. On 9 December the pain in the right hypochondrium suddenly intensified, spread over the abdomen and was associated with vomiting. On examination the BP was 80/50 mmHg. The abdomen was distended with guarding and rebound tenderness. Bowel sounds were sluggish. The right flank mass could not be felt and no fetal heart sounds were elicited. Catheterisation showed frank haematuria. A provisional diagnosis of internal bleeding was made. Hb was 104 g/l; urea, creatinine and electrolytes were normal. Ultrasound confirmed the intrauterine fetal death and showed a distorted right kidney with free fluid in the peritoneal cavity (Fig.).

Artificial rupture of the membranes revealed clear fluid and laparotomy was performed. The peritoneal cavity contained about 300 ml of blood and there was a huge retroperitoneal haematoma around the right kidney. A lower segment Caesarean section was done with delivery of a dead fetus. Exploration of the right kidney showed rupture of the renal parenchyma at the upper pole, the pelvis being full of blood clots. Right nephrectomy was performed. The patient made a good recovery. Intravenous urography confirmed a normal left kidney.

## Comment

Spontaneous rupture of the kidney is uncommon and until 1985 only 13 cases had been reported

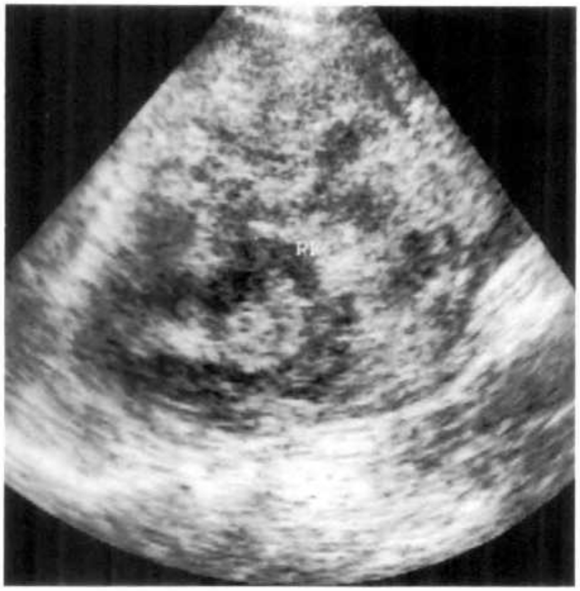

Fig.

(Meyer *et al.*, 1985). Non-traumatic rupture of the kidney during pregnancy may mimic a number of obstetric and surgical emergency situations.

Dilatation of the urinary collecting system during pregnancy is well documented (Harrow *et al.*, 1946) and the distended system is subject to changes in posture and increases in intra-abdominal pressure which predispose to rupture at points distorted by infection or scars.

Rupture of the renal parenchyma usually tears the renal capsule; blood and urine enter the perirenal fat and produce a palpable mass in the flank. The blood and urine dissect along the fascial plane and produce an extensive retroperitoneal haematoma which may break through the peritoneum and lead to peritonitis. The blood may also enter the collecting system, producing haematuria.

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Requests for reprints to: D. A. R. El Halabi, P.O. Box 51619, Rikka, 53457 Rikka, Kuwait.

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# Urethral Adenocarcinoma with High Levels of CA19–9 in Serum and Tumour Specimen

N. MORIYAMA, A. OKAZAWA, K. TOYAMA, T. KITAMURA, I. MURAHASHI, Y. ASO and K. MORIGUCHI,
*Departments of Urology, Branch Hospital, University of Tokyo and Nerima General Hospital, Tokyo, Japan*

## Case Report

A 61-year-old Japanese female with a 6-month history of gross haematuria was found to have diffuse urethral induration (5 × 3 × 3 cm) with a vaginal ulcer. The bilateral inguinal lymph nodes were swollen. Biopsies of the anterior vaginal wall and inguinal nodes showed adenocarcinoma. Computed tomography revealed tumour invasion to the bladder. Serum CA19–9 was 530 u/ml (normal level < 37 u/ml). She was referred to this hospital for pelvic exenteration and regional lymphadenectomy. The urethral surface was replaced by diffusely infiltrating tumour which had penetrated the vagina. The cervix was intact. The pathological diagnosis was well differentiated adenocarcinoma. CA19–9 was found to be diffusely expressed in the cytoplasm and on the luminal surface of glandular/tubular nests, using antibody from Toure Fuji Bionics Co., Japan (Fig.). Serum CA19–9 (maximum 743 u/ml) had returned to normal levels 2 weeks postoperatively. Eight months later, it rose to 68 u/ml as a result of pelvic metastases.

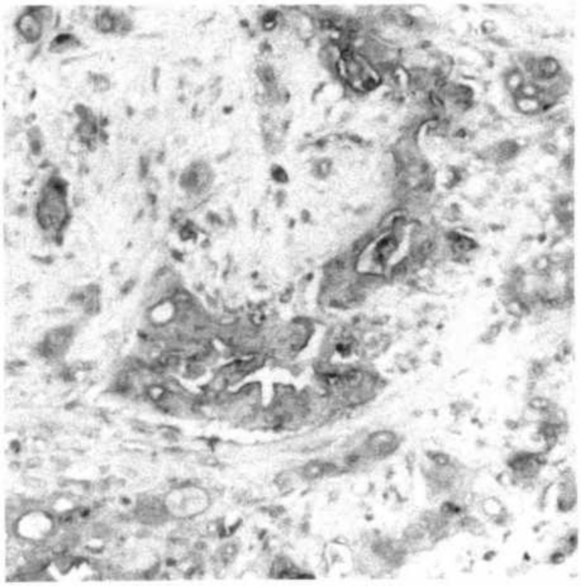

**Fig.** Well differentiated adenocarcinoma (tubular type) cell showing positive staining to anti CA19–9 antibody. ( × 250).

## Comment

Adenocarcinomas, which constitute 10% of primary urethral tumours in women, are divided into 2 types: clear cell and columnar/mucinous (Meis *et al.*, 1987). CA19–9 is known as a tumour marker in pancreatic, hepatobiliary and colorectal malignancy. It can also be detected in patients with carcinoma of the bladder and prostate (Abel *et al.*, 1987). A urethral tumour showing high levels of serum CA19–9 has not previously been reported. This marker may be useful in assessing prognosis, since our patient showed increased levels following the recurrence of metastases.

## References

**Abel, P. D., Cornell, C., Buamah, P. K.** ***et al.*** (1987). Assessment of serum CA19.9 as a tumour marker in patients with carcinoma of the bladder and prostate *Br. J Urol*, **59**, 427–429.

**Meis, J. M., Ayala, A. G. and Johnson, D. E.** (1987). Adenocarcinoma of the urethra in women. A clinicopathologic study *Cancer*, **60**, 1038–1052.

Requests for reprints to: N. Moriyama, Department of Urology, Tokyo University Branch Hospital, 3-28-6 Mejirodai, Bunkyo-ku, Tokyo 112, Japan.

*British Journal of Urology* (1991), 67, 222
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# Notices

## Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

## Dantec Urology Prize

An annual prize is awarded by Dantec for the best scientific paper contributing towards the understanding of the function of the urinary tract, which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will be known as The Dantec Award for Contribution to the Understanding of Urinary Tract Function. The prize will consist of a £400 travel voucher together with a token presentation gift. The prize will be presented at the BAUS Annual Meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered. Three members of BAUS Council will be nominated at the February meeting of Council to act as adjudicators. All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to the Honorary Secretary of the British Association of Urological Surgeons. The winner of the prize will be announced at the Annual Meeting, when the official presentation will be made.

## Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000 to support a clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. Entries will be judged by three members of Council nominated at the February meeting and the winner will be announced at the Annual General Meeting.

## British Association of Urological Surgeons

**President:** R. E. Williams, MD, ChM, FRCS, FRCSE

*Annual Meeting: Glasgow. 25–28 June 1991*

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

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# Diary

1991

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|---|---|
| February 23–March 2 | Royal Society of Medicine, Section of Urology, Vail, Colorado. Contact: M. H. Ashken, Consulting Rooms, BUPA Hospital, Old Watton Road, Colney, Norwich NR4 7SZ. |
| February 24–27 | The American Institute of Ultrasound in Medicine, 35th Annual Convention, Atlanta. Contact: American Institute of Ultrasound in Medicine, 4405 East-West Highway, Suite 504, Bethesda, MD 20814, USA. |
| March 8–9 | Urology for the FRCS. Contact: Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London, WC2H 8JE. Tel: 071 240 9115. |
| March 11–15 | Uro-Andrology Course including Male Infertility and the Management of Impotence. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| March 16–17 | International Symposium of Operative Andrology. For further details of this course and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| April 4–6 | Senior Registrars' Meeting (SURG), Cambridge. Contact: Mr I Eardley, Dept of Urology, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ. Tel: 0223 245151. |
| April 4–5 | Annual Meeting and Teaching Course—Urological Computing Society. Contact: Lindsay Morrison, Membership Secretary, Urological Computing Society, Southern General Hospital, Glasgow, G51 4TF. |
| April 8–28 | Short Courses in Urology and Nephrology including: The Management of Benign and Malignant Prostatic Disease, Paediatric Urology, The Management of Urological Cancers, Tropical Diseases and GU Medicine, Reconstructive Surgery. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| April 24–28 | 1991 Duke Urologic Assembly. St Thomas, US Virgin Islands. Contact: Linda Mace, Assembly Coordinator, Box 3707, Duke Medical Center, Durham, NC 27710, USA. |
| April 26 | Bradford Urology Symposium. Bradford Royal Infirmary. Contact: Mr G. M. Flannigan, Bradford Royal Infirmary, Bradford BD9 6RJ. |
| April 12–13 | Second Meeting of European Society of Paediatric Urology, Beaune, France. "Neurogenic Bladder in Children and Adolescents". Contact: Dr P. Mouriquand, "Le Dizenier", 11 Impasse Mouillard, 69009 Lyon, France. |
| April 14–19 | Forty-fourth Annual Scientific Meeting of the Urological Society of Australasia, Sheraton Mirage Hotel, Gold Coast, Queensland, Australia. Contact: G. Holmes, President, Brisbane Urology Clinic, 11th Floor, 149 Wickham Terrace, Brisbane, QLD 4000. |

| | |
|---|---|
| May 3–4 | Third International Meeting of Andrology<br>Non-surgical Treatment of Impotence. Rome, Italy. Contact: Dr R. Vanzetti, MEDICON ITALIA srl, Piazza Mancini, 4, 00196 Rome, Italy. |
| May 30–31 | **Surgical Andrology, St Bartholomew's Hospital, London. Contact: BAUS Office.** |
| May 25–26 | Fifty-sixth Congress of the Societe Belge d'Urologie, Brussels, Belgium. Contact: F. F. Wart, C.H.U.–I.M.C.A.G., Division of Urology, Bd Zoe Drion, 1, B.6.000 Charleroi–Belgium. |
| June 2–6 | American Urological Association, Metro Toronto Convention Centre, Toronto, Canada. |
| June 7–8 | Fourth Pediatric Surgery Research Workshop, Berlin, Germany. Contact: Dr F. Schier, Pediatric Surgery, Univ.-Klinikum Steglitz, Hindernburgdamm 30, 1000 Berlin 45, Germany. Tel: (0 30) 7 98 41 81/29 09. |
| June 12–15 | Congress of the Portuguese Association of Urology. Funchal, Madeira Island. Contact: Dr Manuel Mendes Silva, Rua Consiglieri Pedrosa, 123, 2745 Queluz, Portugal. Tel: (351-1) 4354044/9. |
| June 16–20 | Canadian Urological Association Annual Meeting, Ottowa. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6. |
| June 17–22 | Diploma Course Revision Block. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| June 18–22 | Tenth World Congress for Sexology, Amsterdam, The Netherlands. Contact: Congress Secretariat, 10th World Congress for Sexology, c/o RAI Organisatie Bureau Amsterdam bv, Europaplein 12, 1078 GZ Amsterdam, The Netherlands. |
| June 25–28 | BAUS Annual Meeting, Scottish Exhibition and Conference Centre, Glasgow. Contact: BAUS office. |
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| August 21–23 | Edinburgh Urological Festival. Contact: Urological Festival Secretary, Department of Surgery/Urology, Western General Hospital, Crewe Rd, Edinburgh EH4 2XU. |
| August 25–31 | First Urology Summer Forum, Oosterbeek. Contact: Secretariat Organization, PO Box 226, 3830 AE LEUSDEN, The Netherlands. |
| September 1–6 | 6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96. |
| September 4–7 | Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllői ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016. |
| September 16–19 | Second Beijing International Symposium on Recent Advances in Urology, Beijing, China. Contact: Gu Fang-liu, Institute of Urology, Beijing Medical University, 1 Da Hong Luo Chang, West District, Beijing 100034, China. |

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British Journal of Urology (1991), 67, 225–229

REVIEW

# Artificial Sphincters

A. R. MUNDY

*Department of Urology, Guy's Hospital, London*

There are few long-term, non-fatal medical conditions that are as disastrous as total urinary incontinence, or indeed as common. The social effect of incontinence on the professional lives of affected patients and the financial consequences for health services are enormous. Of the various causes of urinary incontinence, sphincteric incompetence is one of the most common. Fortunately most patients with sphincteric incompetence have "simple stress incontinence" which generally responds well to one of the many types of bladder neck suspension procedure.' For those with other causes of sphincteric incompetence and for those with "simple stress incontinence" that has failed to respond to a standard anti-stress incontinence procedure there is little to offer except implantation of an artificial urinary sphincter (AUS).

## How an artificial sphincter works

Only one AUS will be considered—the one produced by American Medical Systems (AMS) and generally known as the (Brantley) Scott artificial sphincter (Scott *et al.*, 1973). The Kaufman (1973) and Rosen (1976) devices are of historical interest only.

There are currently 2 models of the AMS device in existence—the AS 800 and its predecessor the AS 792. Both work on the same principle. The device consists of a cuff that is wrapped around a selected point of the bladder outflow, which is connected to a pressure regulating balloon via a control pump (1 component in the AS800; 2 separate components—control assembly and pump—in the AS 792). The entire system is fluid-filled and works hydraulically. The pressure in the system and therefore the occlusive force of the cuff is determined by the pressure regulating balloon and the pressure this produces is related to the physical characteristics of the wall of the balloon. Pressure regulating balloons are manufactured so that when filled to a volume of 16 to 24 ml they produce a pressure within a defined range. This pressure is maintained in the system except when the pump is squeezed. Squeezing the pump rapidly empties the fluid from the cuff into the pressure regulating balloon, thereby removing the occlusive force and allowing voiding to take place. The cuff is kept empty for long enough to allow complete emptying by virtue of a series of delay resistors in the control system between the balloon and the cuff that slow up the refilling of the cuff for 2 to 3 min.

### *Problems with the artificial sphincter*

This simple hydraulic system works well and device malfunctions, either short-term or long-term, are uncommon. Indeed although one would expect, because it is an artificial device, that it would have a finite life span, there is no evidence at present that this is so. It is interesting to speculate as to the reasons why there are few if any competitors for the AMS devices despite several attempts by manufacturers in recent years to produce one. It may be that AMS is the only company that has overcome the problems of reliability and durability.

This is not to say that the AS 800 is free of problems (Nurse and Mundy, 1988). The first and most obvious problem is that it is expensive and it is that more than any other consideration that needs to be addressed in order to make the device available to a wider proportion of incontinent patients. Market competition may eventually help to solve this problem.

Second, the function of the cuff could be improved by making it on a curved rather than a flat template. This would produce a cuff with a single curved compressive cushion rather than a triple cushion as

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at present. This would improve pressure transmission and, by eliminating creases, improve the longevity of the device. (Cuff leaks are the commonest cause of device malfunction and these tend to develop in creases).

Third, the device is not designed to correct for surges in intra-abdominal pressure, so stress incontinence can occur. This is also correctable.

Fourth, the pressure regulating balloons produce a pressure within certain ranges (51–60, 61–70 or 71–80 cm $H_2O$) but the exact pressure is unknown. If this pressure proves to be insufficient, because the patient has persistent incontinence, and the balloon is replaced by one with a higher pressure range, then the change in pressure could be as little as 1 cm $H_2O$ or as high as 19 cm $H_2O$. It would seem reasonable to expect pressures to be defined more precisely.

Finally, there is no way to alter the pressure within the system except by reoperating to exchange the pressure regulating balloon for one with a higher pressure range. This too is correctable—an access portal with a self-sealing membrane could be incorporated into the device. This could then be needled transcutaneously to measure and adjust the pressure in the system precisely.

Despite these comments it must still be acknowledged that if a patient has a type of incontinence for which an AUS is the only option and the symptoms are severe, then the results of AUS implantation are very good. The key to getting good results is patient selection (Mundy and Stephenson, 1984).

## Patient selection—urodynamic considerations

First and foremost it must be realised that an AUS is a treatment for sphincteric incompetence and only that. The principal error in selection of patients for implantation of an AUS is to overlook an abnormality of detrusor function, or to fail to treat it before implanting an AUS (assuming of course that an AUS is indeed indicated), or, worst of all, to implant an AUS despite a known detrusor dysfunction.

The first step therefore is to prove that a patient has sphincteric incompetence and to identify any other coexisting urodynamic abnormality, particularly detrusor overactivity (instability or hyperreflexia). If there is detrusor overactivity this should be treated. As a general rule when detrusor overactivity and sphincter weakness coexist the detrusor overactivity, however mild it may seem, is more important in causing the patient's incontinence unless the sphincter weakness is particularly severe.

Most patients who are considered for implantation of an AUS will fall into 1 of 5 groups—neuropathic bladder dysfunction (mainly congenital), post-prostatectomy incontinence, failed anti-stress incontinence surgery, congenital anomalies and trauma. In neuropathic bladder dysfunction pure sphincteric weakness is rare and detrusor dysfunction, often requiring surgery as well, is almost the rule. This can be demonstrated on pre-operative urodynamic evaluation.

In post-prostatectomy incontinence detrusor instability is also common. Indeed it is the most common abnormality seen (Mundy and Stephenson, 1984). Sometimes however, particularly when sphincter weakness is severe, the detrusor instability may not be apparent on urodynamic investigation until *after* implantation of an AUS. The clue to its presence is, of course, the symptom of urgency before the prostatectomy. Such a patient should be warned that detrusor instability may be present and may cause problems after AUS implantation. Indeed it is best to warn all patients of this possibility.

Most severe "stress incontinence" problems are due to a combination of sphincter weakness and detrusor instability and here, as in post-prostatectomy incontinence, the instability is usually the main problem and correction of that usually leads to the sphincter weakness becoming insignificant. The urethral sphincter mechanism seems much more capable of containing urine in a low pressure bladder than it does in one in which the pressures are even marginally raised.

Congenital anomalies include exstrophy, epispadias and the urogenital sinus/cloacal malformations. In most of these the bladder is either low or normal pressure. The main exception is exstrophy, where the bladder is often thick walled and high pressured.

Traumatic sphincter weakness is usually the result of pelvic fracture injury. Such an injury may also affect the bladder in 1 of 2 ways—either by damage to its innervation or, if the injury also causes a urethral stricture, by secondary obstructive effects.

Thus, in most patients it is possible to predict if they are likely to have detrusor dysfunction even if urodynamic investigation does not reveal it. This does not mean that urodynamic studies are unnecessary; indeed they are mandatory. What it does mean is that problems should be anticipated in such patients despite normal urodynamic studies as they may become apparent only after correction of the sphincteric incompetence.

### Patient selection—identification of high risk categories

In addition to these urodynamic considerations there are 2 other considerations that have to be taken into account during patient selection. The first is the identification of patients who are particularly prone to sphincter-related complications, specifically infection-erosion. Infection and erosion are grouped together because the one inevitably leads to the other, because it is often impossible to determine which came first, and because the treatment of both is the same—removal of the device.

Assuming adequate pre-operative and per-operative measures to minimise the risk of contamination, the absence of per-operative trauma to either the device or the patient's lower urinary tract, and the absence of identifiable risk factors, the infection/erosion rate is 2% (Nurse and Mundy, unpublished data). Four risk factors have been identified with infection-erosion rates that are considerably higher. In neuropathic bladder patients the infection-erosion rate is 15%; in patients who have had failed sling surgery it is 67%; after previous radical pelvic radiotherapy it is 57%; and when an AUS cuff is implanted close to a previous or current suture line in the urinary tract it is 33% (Nurse and Mundy, unpublished data).

Having identified these at-risk groups it is possible to reduce the complication rate in each. For instance, if gross ammoniacal dermatitis is cleared by catheterisation (to allow the skin to dry out) and by appropriate dermatological treatment, the infection-erosion rate in neuropathy is reduced; and if all previous or present suture lines are wrapped with omentum or similar tissue to keep them away from an AUS cuff this risk factor too can be reduced. To a certain extent omental wrapping will also reduce the complication rate in the "sling" and the "radiotherapy" groups but much less so. For this reason I would not use an AUS in such patients unless the patient was, in the radiotherapy group, male and the cuff could be implanted around the bulbar urethra. Even then the infection-erosion rate is 20%.

### Patient selection—selecting the right patient

Another most important factor to consider, discussed last as it is so nebulous, is the patient as an individual. Adequate intelligence, manipulative skills and motivation are obviously important not only to understand how to use the device but to do so competently. Indeed in all reconstructive urological surgery the patient must really want to be treated in order to achieve the best results. If the patient lacks adequate motivation then an AUS should not be forced on them. This particularly applies to children who may themselves be disinterested in their incontinence but who may have determined parents who are extremely keen for the incontinence to be treated. It is important to treat the child and not the parents, because if the child does not use the device properly, complications are sometimes encountered that make the situation even worse.

### Alternatives to AUS implantation

There are 3 main alternatives to AUS implantation—bladder neck reconstruction, urinary diversion (particularly continent urinary diversion) and non-prosthetic anti-stress incontinence surgery.

Standard non-prosthetic anti-stress incontinence surgery works well for "simple stress incontinence" in the generally accepted sense of the term. If one accepts that "simple stress incontinence" is due to 2 factors—loss of urethral support and weakness of the urethral sphincter mechanism—and that standard surgery aims to correct only one, the loss of urethral support (much the most important factor in most patients), then the role of the AUS in anti-stress incontinence surgery could be said to be a means of correcting urethral sphincter weakness in those unusual cases where that is the predominant factor.

Unfortunately non-prosthetic surgery does not work predictably well for other types of sphincter weakness incontinence in which sphincteric incompetence is the only problem and loss of urethral support is irrelevant (whether or not present). In such circumstances (neuropathic, post-prostatectomy and congenital) an AUS is usually necessary.

It is (or should be) a basic tenet of anti-incontinence surgery that an AUS should not be implanted when an alternative non-prosthetic procedure could be expected to be just as successful. The potential for unnecessary implantation of an AUS principally arises with stress incontinence. There is no place for an AUS in the first-line treatment of stress incontinence. If a patient has persistent or recurrent incontinence after previous surgery, which is urodynamically proven to be due to sphincteric incompetence, the crucial factor is whether or not there is (as is usually the case) clinical evidence of persistent or recurrent loss of urethral support. If there is then this should be corrected in the usual way. If not then pure sphincter weakness can be inferred and AUS implantation is reasonable.

Bladder neck reconstruction (or sphincteroplasty as it is sometimes called) could be regarded as another way of avoiding unnecessary prosthetic surgery but it is not really reasonable to compare it with conventional anti-stress incontinence surgery, which has a well established track record of cure. It is principally used in paediatric urology to correct congenital structural or functional incompetence of the bladder neck. It is not very successful, at least not when assessed by the objective urodynamic criteria by which other anti-incontinence procedures are judged, unless it causes frank bladder outflow obstruction and the patient empties thereafter by intermittent self-catheterisation. Even then there is a tendency for the bladder neck reconstruction to "undo itself" with time, although this is mainly a complication in exstrophy bladders that are thick walled, high pressure and low capacity.

Continent urinary diversion is the main way in which reconstructive surgery is avoided these days and lack of availability of an AUS to correct sphincteric incompetence is one reason why some patients will have a substitute bladder drained through a catheterisable track to the abdominal wall rather than emptied spontaneously through the more natural track to the external urinary meatus.

There are undoubtedly instances when a bladder neck reconstruction would be preferable to implantation of an AUS but in general it is to the advantage of most patients undergoing a bladder neck reconstruction to have the cuff of an AUS implanted at the same time so that it is there to connect to the remainder of the AUS components if incontinence persists.

Continent diversion also has a role—typically in a patient whose bladder is ideal for clean intermittent self-catheterisation but whose urethra is uncatheterisable. To use the technique simply because funds are unavailable to buy an AUS would seem inappropriate.

## Results of AUS implantation—general

At Guy's Hospital we have 200 patients followed up for a minimum of 1 year (Nurse and Mundy, unpublished data). Altogether 95% have eventually become continent and 5% are persistent failures. Early on we had yet to learn the importance of correcting "subclinical" detrusor overactivity, so there were complications related to this that we usually now avoid. With this proviso we now expect 72% to be continent to their satisfaction after AUS implantation with no further surgical intervention. (This includes all types of patients—those having just AUS implantation, those having a total pelvic visceral reconstruction including an AUS, and a wide spectrum between). A further 7% will be very much better with their AUS but have an irritating degree of stress-type incontinence that can be corrected by a change of pressure regulating balloon for one with a higher range—this particularly applies to the post-prostatectomy group. A further 11% will be satisfactory after correction of some other complication, usually removal of an infected-eroded device and reimplantation at a later date—this particularly applies to the neuropathic group. Finally, 5% will develop an infection of the AUS requiring its removal but will remain continent after its removal. This group of patients will have been continent with the device before its removal but will have required intermittent catheterisation to empty and will continue to require intermittent catheterisation after removal of the device. Presumably these patients remain continent because an obstructive fibrous sheath develops at the site of the cuff.

Other than the 15.5% infection-erosion rate and the 7% requirement to raise the pressure mentioned above, the other complications are 2% early malfunction, 2% long-term failure rate (due to cuff leakage), 2% technical failure rate (surgical "erosion", tubing kink) and 1% miscellaneous problems unrelated to the device.

## Results of AUS implantation—in relation to aetiology

The neuropathic bladder group is the largest in most series. It is the group with the highest incidence of associated urodynamic problems requiring specific corrective treatment in their own right. It is also the group with the highest incidence of AUS-related complications. One in 3 patients requires further surgery for a complication, either for infection or erosion, or to implant a pressure regulating balloon with a higher range.

Post-prostatectomy incontinence is the most satisfactory group to treat. Complications are rare but 1 in 7 patients requires further surgery to change the pressure regulating balloon for one with a higher range.

Women who have stress incontinence that has failed to respond to standard non-prosthetic surgery also do very well with no significant complications or reoperation rate as long as patients who have had previous sling surgery or radical pelvic radiotherapy are excluded. An AUS is contraindicated in these patients and alternative procedures should be used.

Patients with congenital or traumatic causes of sphincteric incompetence do well as long as precautions are taken to keep the components away from any suture line, past or present. If the proposed cuff site is scarred, has a suture line or is in any other way compromised, it should first be wrapped with omentum and the cuff implanted around the omental wrap. With this proviso the complication rate and reoperation rate are low.

## Conclusions

The availability of an effective AUS has revolutionised reconstructive urology, second only in impact to the introduction of clean intermittent self-catheterisation. The presently used AMS device is reliable and durable and problems with it are relatively trivial. Other than improving the design and function of the device in the way pressure is transmitted and adjusted, major changes seem unlikely and unnecessary in view of the immediate malfunction rate and long-term failure rate of only 2% each. Similarly, the technical complication rate of 1% is also unlikely to improve if surgeons in training are to be taught the techniques of implantation.

The one problem that needs to be attended to is that of infection in patients with neuropathic bladder dysfunction. Other than the pre-operative elimination of ammoniacal dermatitis and scrupulous attention to pre-operative preparation (which is already a considerable ordeal for the patient), one possible solution would be antibiotic coating or impregnation of the device during manufacture or the implantation of antibiotic beads around the device.

Best of all, to avoid the infection-erosion and other problems altogether, would be the development of a non-prosthetic technique to correct sphincteric incompetence which gives equally satisfactory (or better) results. Continent diversion is clearly not the answer—a stoma by any other name is still a stoma. Equally, however loudly the enthusiasts proclaim the *subjective* results of bladder neck reconstruction and "sphincteroplasty" whilst simultaneously deploring the *objective* results of AUS implantation, there is still no non-prosthetic technique that *reliably* or *predictably* gives *objective* results as good. This is not to say that the AUS is a universal panacea for it is not, not even if one strictly limits the discussion to pure sphincteric incompetence without any complicating factors. There are several options available in many patients with sphincter incompetence of which the AUS is only one. But for most properly selected patients and in most properly assessed clinical situations the AUS will usually be the technique of choice if only because there is little else to offer patients in the 2 largest groups—neuropathy and post-prostatectomy. Those who attempt to practise reconstructive surgery of the lower urinary tract without implanting an AUS will find themselves somewhat restricted.

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# The Influence of Diet on Urinary Risk Factors for Stones in Healthy Subjects and Idiopathic Renal Calcium Stone Formers

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Summary—The daily intake of 103 recurrent idiopathic calcium stone formers and 146 controls was assessed by means of a computer-assisted 24-h dietary record. Timed 24-h urine samples were collected over the same period to assess the relationship between dietary intake of nutrients and urinary risk factors for calcium stones. After standardisation for sex, age and social status a total of 128 subjects underwent final statistical analysis; 64 renal stone formers and 64 controls. Significant increases in the consumption of animal and vegetable protein and purine were identified as the nutritional factors that distinguished renal stone formers from controls. As expected, the daily urinary excretion of calcium and oxalate was higher and the daily urinary excretion of citrate was lower in stone formers than in controls. No difference with respect to daily urinary uric acid excretion was recorded. Daily urinary excretion of calcium was correlated to dietary protein intake, while daily urinary oxalate was correlated to dietary vitamin C intake. It was concluded that renal stone formers could be predisposed to stones because of their dietary patterns. A link between the protein content of the diet and urinary calcium was confirmed, but dietary animal protein had a minimal effect on oxalate excretion.

Dietary patterns have been implicated as major contributors to the high prevalence of upper urinary tract stones in affluent countries. A number of nutrients may influence the excretion of calcium, oxalate, urate and citrate predisposing to calcium stone formation (Robertson, 1987): they include increased consumption of protein, refined carbohydrate, calcium, sodium and magnesium and decreased intake of phosphate and dietary fibre.

A high intake of purine or ascorbic acid could increase urinary uric acid and urinary oxalate levels and changes in urinary citrate were reported in patients with reduced protein intake (Goldfarb, 1988). Thus there has been growing interest in measuring the levels of nutrient intake and the excretion of lithogenic and inhibitory substances in renal stone formers and controls. In many of the studies the selection of the control group was inadequate (Coe *et al.*, 1976; Robertson *et al.*, 1979a and b), whereas the studies in which the controls were matched for age, sex and social status failed to detect any significant difference between the dietary intake of the calcium stone formers and controls (Griffith *et al.*, 1981, 1986a and b; Power *et al.*, 1984; Wasserstein *et al.*, 1987; Fellstrom *et al.*, 1989).

The aim of the present study was to compare the dietary intake of calcium renal stone formers and controls before and after standardisation for age, sex and social status. A comprehensive analysis was also performed of the relationship of some nutrients to the 24-h urinary concentrations of lithogenic and inhibitory substances.

## Patients and Methods

The cases comprised patients attending our outpatient stone clinic with recurrent idiopathic calcium stone disease. Patients were excluded if

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they had known aetiological factors such as hyperparathyroidism, renal tubular acidosis and other specific diseases.

The controls were chosen at random from the records of a family doctor but were excluded if they had a history of kidney stones or a history or evidence of any disease or abnormality which could predispose to kidney stones.

Data were obtained on 103 cases (65 male and 38 female) and 146 controls (68 male and 77 female). The median age of the male cases was 46 ± 12 years (range 24–70) and of the female cases 46 ± 14 years (range 19–75); the median age of male controls was 39 ± 13 years (range 19–72) and of female controls 41 ± 13 years (range 20–73). All subjects were questioned about a family history of stone disease, their own past and present medical history, social status and employment.

Participants completed a 24-h dietary record and 24-h urine samples were taken over the same period. Both cases and controls recorded their food intake for the same day of the week. To allow for the time lag between ingestion and urinary excretion of nutrients the early morning urine sample on the day of dietary recording was discarded. All subjects collected 24-h urine from 0700 on the day of dietary recording to 0700 on the following day.

Nutrients and calories were calculated by means of food composition tables using a computerised procedure. Sodium, potassium, calcium, magnesium, zinc, phosphate, oxalate, urate, glycosaminoglycans, creatinine levels and pH were measured in the urine. Sodium and potassium were determined by flame photometry, calcium by a Corning 940 calcimeter, magnesium and zinc by atomic absorption, urinary pH by a Corning pH meter, and phosphate, urate, citrate, glycosaminoglycans and creatinine by colorimetric methods. Total urinary nitrogen excretion was estimated by the sum of urea, creatinine, urate and ammonia and considered a reliable index of dietary protein intake on the assumption that blood urea nitrogen was stable and that both cases and controls were in neutral nitrogen balance. Body mass index was calculated by weight and height (kg/m$^2$).

Means were computed and compared by Student's non-paired *t* test using Statistical Programs for the Social Sciences (SPSS). Additional SPSS programs for regression analysis were used. This analysis was conducted on the group as a whole and on the male and female subgroups. Cases and controls with a family history of renal stones were compared with those with no family history. Finally, to avoid bias for age, sex and social status, the comparison was repeated after standardisation for age, sex and social background.

## Results

The average body mass index was similar in cases and controls, as was the proportion of obesity, defined by a body mass index over 25 kg/m$^2$ for males and 23.8 kg/m$^2$ for females.

Table 1 shows the occupations of cases and controls. There was a smaller proportion of controls compared with cases, whose work was manual; this difference was statistically significant ($\chi^2 = 17.37$, $P < 0.01$).

**Table 1** Distribution of Cases and Controls according to Occupation

| | *Cases (%)* | *Controls (%)* |
|---|---|---|
| Farmers | 0 (0) | 5 (4) |
| Manual workers | 11 (10.5) | 28 (19) |
| Skilled manual workers | 1 (1) | 9 (6) |
| Self-employed workers | 11 (10 5) | 18 (12) |
| Clerks | 42 (41) | 34 (23) |
| Managers | 6 (6) | 5 (4) |
| Pensioners, widows and unemployed | 32 (31) | 47 (32) |

Figures 1 and 2 show the correlation between food intake estimated by 24-h dietary recording and the urinary excretion of corresponding nutrients in the study group as a whole. The daily protein intake was significantly correlated to urinary total nitrogen and the daily sodium intake to urinary sodium excretion.

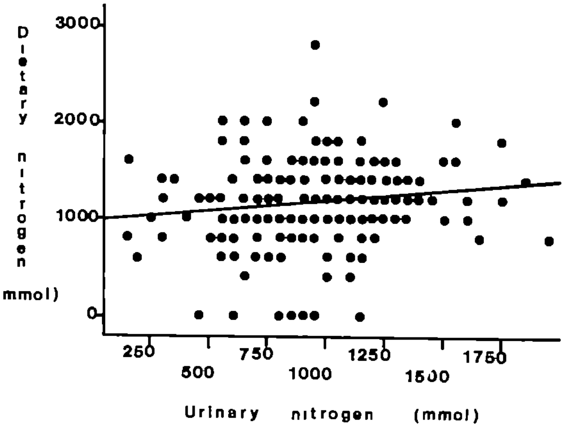

**Fig. 1** Comparison of protein intake estimated by 24-h dietary record and 24-h urinary nitrogen excretion.

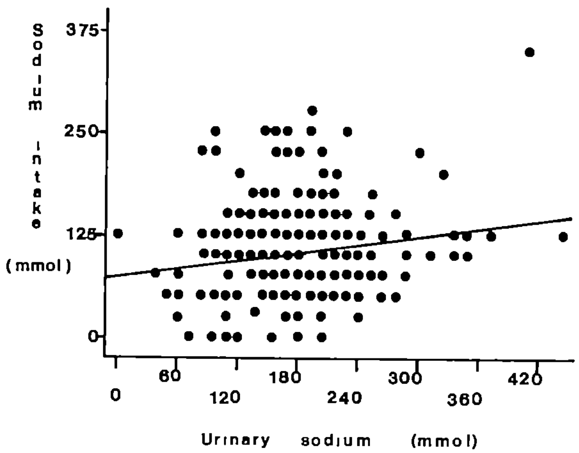

**Fig. 2** Comparison of sodium intake estimated by 24-h dietary record and 24-h urinary sodium excretion.

Tables 2, 3 and 4 list nutrient intakes and urinary risk factors in stone formers and controls unmatched for sex, age and socio-economic background. The daily intake of energy, carbohydrates, fat, protein, purine, calcium and fibre was significantly higher in the stone formers.

Urinary volume, calcium, phosphate, oxalate, glycosaminoglycans and zinc were significantly higher in stone formers than in controls, whereas urinary citrate and magnesium were significantly lower. Among the males, the intake of calories, protein, calcium and fibre was significantly higher in stone formers than in controls; urinary volume, calcium, phosphate, oxalate, glycosaminoglycans and zinc were significantly higher, whereas urinary citrate and magnesium were significantly lower.

In females, there was no significant difference in the dietary intake of the major nutrients in stone

**Table 2** Characteristics of Participants in the Study

| | *Males* | | *Females* | | *Totals* | |
|---|---|---|---|---|---|---|
| | *Cases* | *Controls* | *Cases* | *Controls* | *Cases* | *Controls* |
| No. | 65 | 68 | 38 | 77 | 103 | 146 |
| Age (years) | 46±12 | 39±13† | 46±14 | 41±13 | 45±13 | 41±13† |
| Weight (kg) | 72±12 | 75±9 | 56±16 | 58±9 | 66±16 | 66±12 |
| Height (cm) | 172±6 | 174±6* | 160±6 | 161±5 | 167±8 | 166±8 |
| Body mass index (kg/m²) | 24 5±4.1 | 24.8±3.0 | 22.6±5.4 | 22.4±3.1 | 23.8±4.6 | 23.5±3.3 |

* $P<0.05$, † $P<0.01$.

**Table 3** Dietary Intake in 103 Cases and 146 Unmatched Controls

| | *Males* | | *Females* | | *Totals* | |
|---|---|---|---|---|---|---|
| | *Cases* | *Controls* | *Cases* | *Controls* | *Cases* | *Controls* |
| Calories (kcal) | 2997±791 | 2667±827* | 2649±688 | 2388±812 | 2864±769 | 2514±827‡ |
| Carbohydrate (g) | 295±117 | 265±87 | 257±93 | 237±77 | 281±110 | 250±82* |
| Fat (g) | 138±65 | 119±51 | 130±41 | 111±51* | 135±56 | 114±51† |
| Total protein (g) | 117±37 | 97±32† | 104±34 | 96±27 | 111±36 | 96±29‡ |
| Animal protein (g) | 82±33 | 72±24* | 76±30 | 71±23 | 80±30 | 71±23* |
| Vegetable protein (g) | 33±13 | 28±9 | 27±11 | 26±8 | 31±12 | 26±10† |
| Purine (mg) | 321±293 | 200±119† | 217±189 | 186±109 | 282±262 | 192±113‡ |
| Oxalate (mmol) | 1.06±1.28 | 0.94±0 74 | 0.75±0.74 | 1.14±1.04* | 0.94±1.22 | 1.04±0.91 |
| Vitamin C (mmol) | 0.89±0.56 | 0.84±0.49 | 0.71±0.70 | 0.85±0.52 | 0.82±0.62 | 0.85±0.50 |
| Sodium (mmol) | 127±66 | 112±50 | 102±55 | 102±54 | 117±62 | 106±52 |
| Potassium (mmol) | 70±20 | 68±25 | 64±19 | 67±25 | 68±20 | 68±14 |
| Calcium (mmol) | 29.0±17.3 | 23.2±12.9* | 28.1±18.2 | 24.6±15.0 | 28.7±17.6 | 23.9±14.0* |
| Dietary fibre (g) | 27.4±12.3 | 21.7±8.2† | 21.1±10.2 | 20 2±8 1 | 25.0±11.9 | 20.9±8 1† |
| Phosphate (mg) | 13.9±5.0 | 12.9±4.9 | 13.7±4.6 | 12.5±5.5 | 13.8±4.6 | 12.7±5 2 |

* $P<0.05$, †$P<0.01$, ‡ $P<0.001$.

**Table 4** Laboratory Findings in 103 Cases and 146 Unmatched Controls

| | *Males* | | *Females* | | *Totals* | |
|---|---|---|---|---|---|---|
| | *Cases* | *Controls* | *Cases* | *Controls* | *Cases* | *Controls* |
| Urinary volume (ml/24 h) | 1660±656 | 1158±278‡ | 1610±707 | 988±366‡ | 1642±672 | 1072±340‡ |
| Urinary pH | 5.88±0.40 | 5.86±0.28 | 5.82±0.59 | 5.92±0.41 | 5.87±0.48 | 5.90±0.36 |
| Urinary potassium (mmol/24 h) | 53±21 | 52±17 | 49±16 | 44±14 | 52±19 | 48±15 |
| Urinary sodium (mmol/24 h) | 193±76 | 189±61 | 166±48 | 152±52 | 183±68 | 170±59 |
| Urinary calcium (mmol/24 h) | 6.10±3.12 | 4.90±2.30* | 5.45±2.80 | 4.07±1.95† | 5.87±3.00 | 4.45±2.15‡ |
| Urinary phosphate (mmol/24 h) | 8.35±2.85 | 7.77±2.29 | 7.14±2.50 | 6.18±2.40* | 7.91±2.78 | 6.92±2.28† |
| Urinary urate (mmol/24 h) | 3.01±1.07 | 3.35±1.16 | 2.55±0.87 | 2.69±0.98 | 2.84±1.02 | 3.01±1.11 |
| Urinary oxalate (mmol/24 h) | 0.32±0.10 | 0.22±0.05‡ | 0.32±0.23 | 0.26±0.06* | 0.32±0.15 | 0.22±0.05‡ |
| Urinary magnesium (mmol/24 h) | 2.55±1.35 | 4.32±1.35* | 2.18±1.15 | 3.41±1.89* | 2.38±1.23 | 3.82±1.72† |
| Urinary zinc (μmol/24 h) | 15±15 | 6±3† | 10±5 | 4±2* | 13±5 | 5±3‡ |
| Urinary citrate (mmol/24 h) | 1.56±0.94 | 2.21±0.86‡ | 1.74±0.94 | 2.20±0.80* | 1.62±0.94 | 2.21±0.82‡ |
| Urinary glycosaminoglycans (μmol/24 h)§ | 1.51±0.74 | 1.07±0.35‡ | 1.45±0.55 | 0.82±0.27‡ | 1.48±0.67 | 0.94±0.33‡ |
| Urinary creatinine (mmol/24 h) | 13.5±3.7 | 14.1±3.3 | 9.0±1.8 | 8.8±2.3 | 11.8±3.8 | 11.3±3.8 |
| Urinary urea (Mol/24 h) | 398±140 | 435±153 | 341±113 | 333±115 | 376±133 | 381±143 |

* $P<0.05$, † $P<0.01$, ‡ $P<0.001$.

§ expressed as hyaluronic acid assuming a relative molecular mass of 20,000.

formers compared with controls, except for a lower intake of oxalate and a higher intake of fat in the cases. Urinary volume, calcium, phosphate, oxalate and glycosaminoglycans were significantly higher in female cases than in female controls, whereas female stone formers excreted less magnesium and citrate than female controls.

Tables 5, 6 and 7 compare dietary intake and urinary risk factors in calcium stone formers and controls matched for age, sex and social status. The pattern of differences in dietary intake between cases and matched controls was similar to that observed in the unmatched comparison, but only the differences in protein and purine intake reached high statistical significance. Differences in calories and carbohydrate intake were only significant at the 5% level. Stone formers were found to have higher urinary volume, calcium, phosphate, oxalate, glycosaminoglycans and zinc and lower citrate and magnesium compared with matched controls. Using a multiple regression analysis for the entire series of renal stone formers and controls, we were able to show a statistically significant correlation ($P<0.02$) between protein intake and urinary calcium, vegetable protein intake and urinary phosphate and magnesium, vitamin C intake and urinary oxalate and magnesium, carbohydrate and potassium intake and glycosaminoglycans.

A family history of stones was found more often among cases (34%) than controls (18%) and a positive family history was more common among female (42%) than among male patients (29%).

**Table 5** Characteristics of 64 Cases and 64 Matched Controls

| | *Cases* | *Controls* |
|---|---|---|
| No. | 64 | 64 |
| Age (years) | 45±12 | 45±12 |
| Weight (kg) | 63±18 | 66±13 |
| Height (cm) | 165±8 | 166±9 |
| Body mass index (kg/m²) | 23.4±5.5 | 23.6±3.2 |

**Table 6** Dietary Intake in 64 Cases and 64 Matched Controls

| | *Cases* | *Controls* |
|---|---|---|
| Calories (kcal) | 2816±712 | 2538±718* |
| Carbohydrate (g) | 285±96 | 250±74* |
| Fat (g) | 125±38 | 114±46 |
| Total protein (g) | 111±37 | 93±30† |
| Animal protein (g) | 79±32 | 69±22* |
| Vegetable protein (g) | 31±12 | 27±9* |
| Purine (mg) | 286±288 | 176±112† |
| Oxalate (mmol) | 0.93±1.21 | 1.03±0.83 |
| Vitamin C (mmol) | 0.76±0.64 | 0.92±0.2 |
| Sodium (mmol) | 119±62 | 107±48 |
| Potassium (mmol) | 67±17 | 70±24 |
| Calcium (mmol) | 29.0±17.8 | 24.9±13.7 |
| Dietary fibre (g) | 23.2±10.7 | 20.8±7.4 |
| Phosphate (mmol) | 13.7±4.69 | 12.8±4.78 |

* $P<0.05$, † $P<0.01$.

**Table 7** Laboratory Findings in 64 Cases and 64 Matched Controls

| | *Cases* | *Controls* |
|---|---|---|
| Urinary volume (ml/24 h) | 1668±0.98 | 1045±308‡ |
| Urinary pH | 5.91±0.52 | 5.82±0.30 |
| Urinary potassium (mmol/24 h) | 50±17 | 49±15 |
| Urinary sodium (mmol/24 h) | 138±65 | 165±52 |
| Urinary calcium (mmol/24 h) | 5.85±3.12 | 4.37±2.17† |
| Urinary phosphate (mmol/24 h) | 7.53±2.6 | 6.63±2.04* |
| Urinary urate (mmol/24 h) | 2.68±0.94 | 2.84±0.97 |
| Urinary oxalate (mmol/24 h) | 0.34±0.19 | 0.25±0.03† |
| Urinary magnesium (mmol/24 h) | 2.30±0.90 | 3.78±1.39† |
| Urinary zinc (µmol/24h) | 13±3 | 2±3† |
| Urinary citrate (mmol/24 h) | 1.49±0.91 | 2.22±0.82‡ |
| Urinary glycosaminoglycans (µmol/24 h)§ | 1.46±0.62 | 0.99±0.31‡ |
| Urinary creatinine (mmol/24 h) | 11.13±4.12 | 11.17±3.93 |
| Urinary urea (Mol/24 h) | 365±130 | 360±133 |

* $P<0.05$, † $P<0.01$, ‡$P<0.001$.

§ expressed as hyaluronic acid assuming a relative molecular mass of 20,000.

We found no difference between subjects with a positive family history and those with no family history in their nutrient intake and urinary chemistry, except for a lower dietary intake of oxalate in patients with a positive family history. The relationship between nutrients and the urinary excretion of calcium and oxalate was established separately for cases and controls with a family history of stones and for those with no family history. The correlation coefficients of the regression of urinary oxalate excretion on dietary vitamin C intake (0.26 vs 0.13) and dietary oxalate intake (0.27 vs 0.06) were higher in subjects with a family history of stones than in those with no family history. In subjects with a positive family history of stones the correlations of urinary oxalate excretion with dietary vitamin C intake and dietary oxalate intake were statistically significant, but in those with no family history they were not significant. The correlations of urine calcium excretion with nutrients were weaker in both groups.

## Discussion

It has been claimed that a single interview is an imprecise method of measuring food intake, while the 4-day food diary is more suitable (Power *et al.*, 1984). The 24-h dietary record is imprecise for extrapolating to an individual's lifetime exposure to nutrients but it is a good technique for cross-sectional analyses intended to identify differences among specific populations (McCarron *et al.*, 1984).

The mean dietary intake of protein and sodium estimated by 24-h dietary recording correlated significantly with the mean measured urinary excretion of the corresponding nutrient. We conclude that the 24-h dietary record is a reliable method of assessing dietary intake for a population study.

In the unmatched comparison, the dietary intake of calories, protein, fat, carbohydrates, purine, calcium and dietary fibre was markedly higher in stone formers than in controls. The explanation for this is the predominance of male subjects among the cases, who had a male to female ratio of 1:0.58 compared with 1:1.13 among the controls.

Males had a higher caloric intake and consumed more nutrients than females (Griffith *et al.*, 1986a and b). Furthermore, distribution by social class was different in cases and controls, so the greater affluence among stone formers could have led to a "richer" diet than that consumed by the controls. However, after standardisation for age, sex, and social status we still found significant differences in the dietary intake of animal and vegetable protein and purine, unlike previous matched case control studies (Griffith *et al.*, 1981, 1986a and b; Power *et al.*, 1984; Wasserstein *et al.*, 1987; Fellstrom *et al.*, 1989).

Some control groups consisted of urological patients (Griffith *et al.*, 1981, 1986a and b) or volunteers (Wasserstein *et al.*, 1987).

The present study was confined to recurrent idiopathic calcium renal stone formers, whereas other studies included patients with all types of stones (Power *et al.*, 1984) or even first-time stone formers (Griffith *et al.*, 1986a and b). In a study, differences may have been concealed by the small sample size (Fellstrom *et al.*, 1989).

Several unmatched studies found higher intakes of animal protein among stone formers (Coe *et al.*, 1976; Robertson *et al.*, 1979a and b), but no difference in dietary protein derived from vegetable was found between patients and controls by Robertson *et al.* (1979a and b). This observation contrasts with our results.

A number of reports (Robertson *et al.*, 1978; Robertson and Peacock, 1980; Nicar *et al.*, 1983; Wasserstein *et al.*, 1987) have indicated hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia and low urinary volume as major risk factors for calcium stones.

Urinary volume was unexpectedly higher in stone formers than in controls and perhaps they had been advised to increase their fluid intake by general practitioners and even by other patients prior to our evaluation. We were unable to show any difference in uric acid excretion between stone formers and controls.

In a previous study, reduced urinary excretion of glycosaminoglycans was observed in stone formers compared with controls (Robertson *et al.*, 1978), but other workers found no significant difference (Samuell, 1981; Hwang *et al.*, 1988). Our study, contrary to expectation, showed a higher daily urinary glycosaminoglycans excretion in renal stone formers and no significant difference with respect to the concentration of urinary glycosaminoglycans, but our renal stone formers had a higher mean urinary volume than the controls. A positive correlation between daily urinary glycosaminoglycans excretion and urinary volume has been found in both normal subjects and renal stone formers (Hwang *et al.*, 1988). Furthermore, in renal stone formers a higher protein intake could increase urinary glycosaminoglycans excretion, because this has been positively correlated with urinary sulphate, which is a raw index of the dietary content of animal protein (Hwang *et al.*, 1988). Both magnesium and zinc seem to be important inhibitors of calcium crystal formation. Our results show that in renal stone formers, urinary magnesium excretion was less than normal but zinc excretion was increased. Urinary magnesium deficiency may be a pathogenetic factor in renal stone disease. However, the reports on urinary magnesium in renal stone formers are conflicting: in some studies it was reported to be lower, but in other studies it was equal to or higher than that found in controls (Johansson *et al.*, 1980).

No variation in urinary zinc excretion has been previously reported in renal stone formers, but the increased urinary zinc excretion observed in our patients with calcium stones could be due to the increased dietary animal protein.

It has been suggested that a low fibre diet increases the risk of stone disease and a fall in urinary calcium excretion has been shown after increased dietary fibre consumption (Shah *et al.*, 1980). Our findings in this respect are not in accordance with those of previous studies in which cases had a lower intake of dietary fibre than controls (Griffith *et al.*, 1981, 1986a and b).

As expected, urinary calcium excretion correlated with daily protein ingestion (Robertson *et al.*, 1979a and b).

Dietary protein intake increases net fixed acid production and acid excretion, thus inhibiting renal tubular reabsorption of calcium (Lemann *et al.*, 1986). It has also been suggested that animal protein is a dietary source of oxalate precursor in metabolism (Robertson *et al.*, 1979a and b), but we were unable to show any significant effect of dietary protein on oxaluria.

Finally, information about obesity and familial predisposition towards stone disease was analysed. The link between obesity and calcium stone disease was not confirmed in this investigation and the total caloric intake did not differ consistently between renal stone formers and controls matched for age and sex. A familial predisposition towards stone formation was more common in the female case group, whilst the male cases showed greater differences in dietary intake compared with the male controls. These findings suggest that a "rich" diet makes men more prone to calcium stones than women, whereas metabolic abnormalities play a prominent part in stone formation in women.

In subjects with a positive family history of stones the correlations of urine oxalate excretion with either oxalate or vitamin C dietary intake were stronger than in those with no family history, suggesting either that they absorb more oxalate from the diet or that they metabolise a greater proportion of oxalate precursors (Hodgkinson, 1978). Our results accord with observations demonstrating that idiopathic calcium oxalate stone formers shows a genetically transmitted cellular defect in oxalate transport (Baggio *et al.*, 1984).

Differences in dietary habits are responsible for the geographical differences in stone disease. In particular, the pivotal role of animal protein intake in the aetiology of stones arose from the examination of dietary trends in Northern Europe and North America. In the Mediterranean area, people eat larger amounts of farinaceous food and vegetables and a consumption of excessive amounts of vegetable protein may also be a risk factor.

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# Results of Long-term Rice Bran Treatment on Stone Recurrence in Hypercalciuric Patients

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Summary—A series of 182 calcium stone formers with idiopathic hypercalciuria underwent treatment with rice bran for 1 to 94 months. Urinary calcium excretion was considerably reduced, but there was some increase in urinary phosphate and oxalate. Urinary excretion of magnesium and uric acid, serum calcium, magnesium, phosphate, uric acid, parathyroid hormone (PTH) and ALP was unaffected. There were no obvious changes in serum iron, zinc and copper even when patients were treated for long periods. Rice bran was well tolerated in almost all cases and there were no serious side effects; 49 patients have undergone treatment for more than 3 years (average duration of administration 5.09 years). The frequency of new stone formation was drastically reduced (individual stone formation rate (no./year) from 0.720 ± 0.533 to 0.125 ± 0.204; group stone formation rate (no./patient-year) from 0.721 to 0.120) compared with the 3-year period before treatment. During treatment, 61.2% of patients remained in remission. Although rice bran therapy should be effective in correcting absorptive hypercalciuria, there may be limits to the overall ability of rice bran monotherapy to prevent recurrence.

About 8 years ago we began a clinical trial on the efficacy of defatted rice bran in preventing calcium stone recurrence and have already published some data on the hypocalciuric effect produced from the binding of intestinal calcium by phytin (inositol hexaphosphate) in the rice bran (Ohkawa *et al.*, 1983, 1984; Ebisuno *et al.*, 1986).

We report the results of urine and blood analysis in 182 hypercalciuric stone formers who received rice bran therapy for varying periods of time. The problems caused by long-term administration are noted. We also assessed the clinical effectiveness of rice bran in preventing the development of new stones in 49 patients treated for more than 3 years (average duration of administration 5.09 years).

## Patients and Methods

Rice bran for clinical use was defatted by extraction with n-hexane, cultivated with *Aspergillus oryzae* Cohn and autoclaved, with the following constituents: total phosphorus 3.72 g/100 g, phytate phosphorus 2.67 g/100 g, calcium 0.1 g/100 g, magnesium 1.16 g/100 g, fatty substance 7.4 g/100 g and crude fibre 7.2 g/100 g. The pharmacological details of rice bran were provided by Boso Oil Co. Ltd (Chiba, Japan).

A total of 182 patients with calcium-containing urinary stones (154 males and 28 females) received 10 g rice bran twice daily after meals for 1 to 94 months. All had hypercalciuria (>200 mg/day on ordinary diet) and none had primary hyperparathyroidism, renal tubular acidosis, bone disease or other conditions known to cause hypercalcaemia or hypercalciuria. They were told to follow their usual diet and were followed up periodically at the outpatient clinic.

Biochemical investigations, including determination of serum calcium, phosphorus, magnesium, uric acid and urinary calcium, phosphorus, oxalate, uric acid and magnesium, were performed after 1 and 2 months and, as a rule, at 4-monthly intervals thereafter. In some cases serum ionic calcium, iron, copper, zinc, parathyroid hormone and serum

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alkaline phosphatase were also monitored periodically.

In 49 patients to whom rice bran was given for more than 3 years, the effectiveness of treatment in preventing new stones was assessed as follows. For the 3 years immediately preceding treatment, a retrospective history was taken from each patient regarding the spontaneous passage or surgical removal of stones. Before treatment, the results of radiological examination of the urinary tract were reviewed in order to determine the presence of stones, so that any change in their number and size and the appearance of new stones could be detected during treatment. During treatment, each new stone episode was recorded by direct interview and roentgenogram or ultrasound examination. A new stone episode was represented by the spontaneous passage of a new stone, the appearance of a new stone on serial X-ray films, surgical removal of a new stone or clear growth in size of a pre-existing stone. Spontaneous passage and surgical removal of pre-existing stones were excluded.

The effectiveness of treatment in preventing new stones was assessed according to individual stone formation rate, group stone formation rate and remission rate (Pak *et al.*, 1981). The individual stone formation rate was calculated for each patient as number/year for the period before treatment and during treatment. The group stone formation rate was also calculated as number/patient-year by dividing the total number of stones by the cumulative years for the period of pre-treatment (3 years) and during treatment. The remission rate represented the percentage of patients who formed no new stones during treatment.

The significance of mean differences in laboratory data before and during treatment was evaluated by Student's *t* test.

## Results

The effects of rice bran treatment on urinary biochemistry are summarised in Table 1. Rice bran caused a significant reduction in urinary calcium within the first month and the effect was sustained during treatment. There was some increase in urinary phosphorus and oxalate excretion, but magnesium and uric acid were unaffected.

The results of blood biochemistry are shown in Table 2. There were no changes in serum calcium (total and ionic), phosphorus, magnesium or uric acid. Serum iron, zinc and copper were unaffected even after long-term treatment (Table 3). PTH and serum alkaline phosphatase in some patients were unaffected throughout treatment.

The effect of rice bran treatment on new stone

**Table 1** Effect of Rice Bran Treatment on Urinary Biochemistry

| | *Before treatment* | *After treatment (months)* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | *1* | *12* | *24* | *36* | *48* | *60* | *72* |
| Ca (mg/day) | | | | | | | | |
| mean | 337 | 231* | 235* | 238* | 242* | 254* | 250* | 232* |
| SD | 91 | 79 | 79 | 88 | 70 | 83 | 55 | 80 |
| n | 182 | 136 | 93 | 87 | 41 | 25 | 17 | 18 |
| P(mg/day) | | | | | | | | |
| mean | 843 | 1003* | 1017* | 975† | 998† | 933 | 963 | 914 |
| SD | 312 | 311 | 307 | 277 | 323 | 236 | 358 | 230 |
| n | 182 | 148 | 93 | 87 | 49 | 25 | 18 | 20 |
| Oxalate (mg/day) | | | | | | | | |
| mean | 41.7 | 48.1† | 48.4† | 49.4† | 49.4† | 43.1 | 44.8 | 41.4 |
| SD | 12.8 | 10.6 | 11.6 | 13.6 | 13.6 | 12.2 | 12.8 | 13.6 |
| n | 74 | 53 | 49 | 41 | 27 | 13 | 4 | 10 |
| Mg (mg/day) | | | | | | | | |
| mean | 93 | 97 | 87 | 99 | 94 | 93 | 94 | 106 |
| SD | 33 | 45 | 30 | 45 | 36 | 40 | 57 | 43 |
| n | 131 | 105 | 82 | 74 | 43 | 19 | 8 | 11 |
| Uric A (mg/day) | | | | | | | | |
| mean | 656 | 662 | 626 | 593 | 607 | 566 | 592 | 561 |
| SD | 273 | 511 | 242 | 204 | 186 | 224 | 212 | 180 |
| n | 175 | 148 | 93 | 86 | 48 | 25 | 18 | 20 |

(*: $P<0.001$, †: $P<0.01$, ‡: $P<0\ 05$ compared to pre-treatment value).

**Table 2** Effect of Rice Bran Treatment on Blood Biochemistry

| | *Before treatment* | *After treatment (months)* 1 | 12 | 24 | 36 | 48 | 60 | 72 |
|---|---|---|---|---|---|---|---|---|
| Total CA (mEq/L) | | | | | | | | |
| mean | 4.70 | 4.70 | 4.75 | 4.68 | 4.81 | 4.61 | 4.63 | 4.54 |
| SD | 0.46 | 0.33 | 0.37 | 0.34 | 0.71 | 0.16 | 0.12 | 0.13 |
| n | 182 | 110 | 69 | 64 | 39 | 19 | 16 | 18 |
| Ionic Ca (mEq/L) | | | | | | | | |
| mean | 2.25 | 2.35 | 2.37 | 2.27 | 2.32 | 2.30 | 2.33 | 2.39 |
| SD | 0.13 | 0.06 | 0.12 | 0.08 | 0.09 | 0.11 | 0.16 | 0.11 |
| n | 4 | 4 | 13 | 20 | 13 | 12 | 11 | 15 |
| P (mg/dl) | | | | | | | | |
| mean | 3.17 | 3.18 | 3.28 | 3.22 | 3.03 | 3.09 | 3.11 | 3.14 |
| SD | 0.57 | 0.58 | 0.58 | 0.47 | 0.54 | 0.42 | 0.51 | 0.61 |
| n | 182 | 107 | 68 | 63 | 37 | 19 | 16 | 16 |
| Mg (mg/dl) | | | | | | | | |
| mean | 1.80 | 1.83 | 1.81 | 1.76 | 1.77 | 1.69 | 1.71 | 1.74 |
| SD | 0.33 | 0.33 | 0.30 | 0.28 | 0.27 | 0.37 | 0.25 | 0.32 |
| n | 108 | 89 | 53 | 48 | 36 | 14 | 11 | 16 |
| Uric A (mg/dl) | | | | | | | | |
| mean | 5.55 | 5.63 | 5.46 | 5.42 | 5.03 | 5.09 | 5.50 | 5.02 |
| SD | 1.35 | 1.34 | 1.34 | 1.31 | 1.24 | 1.50 | 0.87 | 1.57 |
| n | 167 | 107 | 69 | 64 | 39 | 19 | 16 | 18 |

**Table 3** Effect of Rice Bran Treatment on Serum Iron, Zinc and Copper

| | *Before treatment* | *After treatment (months)* 1 | 12 | 24 | 36 | 48 | 60 | 72 |
|---|---|---|---|---|---|---|---|---|
| Fe (γ/dl) | | | | | | | | |
| mean | 92.5 | 101.0 | 110.0‡ | 99.3 | 103.0 | 92.7 | 119.0‡ | 116.0‡ |
| SD | 29.7 | 41.6 | 35.0 | 36.5 | 39.0 | 25.9 | 35.2 | 51.1 |
| n | 37 | 44 | 24 | 32 | 24 | 13 | 10 | 16 |
| ZN (γ/dl) | | | | | | | | |
| mean | 81.9 | 88.4 | 85.7 | 78.5 | 81.7 | 74.9 | 87.7 | 79.0 |
| SD | 9.26 | 17.6 | 15.1 | 12.1 | 16.1 | 8.7 | 16.2 | 13.5 |
| n | 8 | 12 | 19 | 21 | 15 | 10 | 11 | 12 |
| Cu (γ/dl) | | | | | | | | |
| mean | 112.0 | 103.0 | 104.0 | 101.0 | 99.2 | 98.9 | 99.0 | 104.0 |
| SD | 11.6 | 19.9 | 13.3 | 17.9 | 13.4 | 16.1 | 17.4 | 17.5 |
| n | 8 | 18 | 21 | 24 | 19 | 13 | 10 | 15 |

(‡: $P<0.05$ compared to pre-treatment value).

formation is shown in Table 4. The average duration of treatment was 5.09 years. An obvious decline, both in the individual and the group stone formation rate, was noted when values were compared with the corresponding pre-treatment values. In 19 patients, 30 new stones were formed during treatment at 10 to 90 months, and in 30 patients (61.2%) the disease has remained in remission.

Although rice bran was not always palatable to all patients, none suffered from severe bowel discomfort. The administration of rice bran had to

**Table 4** Effect on Stone Recurrence in 49 Patients Treated for more than 3 Years

| | *Before treatment (3 years)* | *During treatment* |
|---|---|---|
| Total stones | 106 | 30 |
| Mean duration (yr/pt) | 3.00 | 5.09 |
| Stone formation rate | | |
| No./yr | 0.720±0.533 | 0.125±0.204 |
| No./pt-yr | 0.721 | 0.120 |
| Remission rate (%) | — | 61.2 |

be discontinued in 2 cases because of its unpalatable taste and mild diarrhoea occurred in 4 patients. In a female patient with iron deficiency anaemia, the serum iron level fell and therapy was discontinued at 33 months; following this, the serum iron returned to pre-treatment levels.

## Discussion

We previously reported that rice bran reduced urinary calcium excretion in patients with idiopathic hypercalciuria, especially the absorptive type, with no serious side effects, and that phytin in rice bran played an active role in reducing the intestinal absorption of calcium. Rice bran or phytin had a variable influence on intestinal calcium absorption according to the content of dietary calcium (Ohkawa *et al.*, 1984). The interaction between calcium and phytate in the intestine, which has been studied previously, suggests an adverse effect of high calcium intake on the efficacy of phytate (Krieger and Steenbock, 1940; Taylor, 1965). Thus rice bran treatment is likely to be more effective with an appropriate high calcium intake, and to be more suitable for clinical treatment of hyperabsorptive hypercalciuria without causing calcium deficiency even when patients are treated for long periods of time.

Tizzani *et al.* (1989) found no increase in urinary phosphate using a dietary supplement of 28 g wheat bran; in our series, however, there was an obvious increase during rice bran therapy. The source of the urinary phosphorus is presumed to be the absorbable phosphorus produced from hydrolysis of phytate in the intestine. Thomas and Tilden (1972) suggested that small concentrations of di- and tri-phosphorylated inositol might inhibit the formation of hydroxyapatite crystals in metastable solutions. Modlin (1980) hypothesised that a high content of phosphorylated inositol in the urine could be an effective inhibitor of stone formation. Although a large amount of inositol phosphate available for the inhibition of crystal formation has not been detected in human urine, it is possible that some phosphate from the rice bran has this action in preventing stone formation.

It is well known that idiopathic calcium stone has a multifactorial aetiology. Various physiological abnormalities have been detected in patients, *e.g.* hypercalciuria, hyperuricosuria, hyperoxaluria and hypocitraturia, etc. Some selective treatments have been recommended to correct the abnormal physicochemical environment of urine and physiological disturbances in patients with urinary stones (Pak *et al.*, 1980, 1981). On the basis of our experience, rice bran therapy is effective in correcting absorptive hypercalciuria. However, it has a tendency to increase urinary oxalate and the beneficial effects of rice bran therapy may be compromised if there is no restriction of dietary oxalate.

Approximately 60% of patients with refractory hypercalciuria have remained in remission during treatment and only 40% developed new stones. Initially, we had expected that the hypocalciuric action and increase in urinary phosphorus induced by rice bran treatment would have had a greater effect on stone recurrence. The results of this study lead us to believe that monotherapy, though effective, is limited in its ability to prevent recurrence in active stone formers, and it may be necessary to seek additional treatment for complete prophylaxis.

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# Acute Changes in Kidney Function following Extracorporeal Shock Wave Lithotripsy for Renal Stones

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Summary—Seventeen patients were subjected to analysis of various renal functional parameters before and after extracorporeal shock wave lithotripsy (ESWL) for renal stones. Thirteen patients were observed at 2 weeks and 3 months. Glomerular filtration rate (GFR) was not influenced by ESWL as based on unchanged serum levels of creatinine, $\beta_2$-microglobulin and creatinine clearance. A significant increase in urinary excretion of $\beta_2$-microglobulin, N-acetyl-$\beta$-glucosaminidase and alkaline phosphatase, with return to pre-treatment values within 4 to 5 days, reflected transient disturbances in proximal tubular function. Urinary albumin excretion was increased 0–24 h after ESWL. No significant alterations were observed in plasma renin activity or serum aldosterone due to ESWL. Serum lactic dehydrogenase remained significantly increased for 2 weeks. In addition, significant changes in several blood and urine parameters were caused by immersion in water and intravenous infusions during treatment and were not specifically due to ESWL.

Since the introduction of ESWL to clinical practice (Chaussy *et al.*, 1982), the results of large clinical series have shown that extracorporeal shock wave lithotripsy is effective in stone disintegration.

Side effects, however, do occur. Magnetic resonance imaging (MRI) has detected renal injury in up to 85% of patients (Baumgartner *et al.*, 1987) and several authors have reported morphological and functional changes based on both animal experiments and clinical investigations (Lingeman *et al.*, 1988).

The significance of any physiological change following ESWL is unknown. A causal relationship to the development of hypertension has been postulated in a small percentage of patients (Williams *et al.*, 1987). In our controlled studies on acute renal changes following extracorporeal shock wave exposure to 1 kidney in dogs (Karlsen *et al.*, 1990a and b), changes were detected in glomerular, tubular and renal vascular morphology and function. In the exposed kidney, effective renal plasma flow (ERPF) decreased significantly, while glomerular filtration rate was unchanged. Filtration fraction increased in both kidneys. A non-significant rise in plasma renin activity (PRA), most marked in the renal vein blood from the exposed kidney, was noted. A significant rise in urinary excretion of N-acetyl-$\beta$-glucosaminidase (U-NAG) and fall in the extraction of para-amino-hippuric acid (PAH) in the exposed kidney reflected damage to proximal tubular function.

Despite the extensive use of ESWL, knowledge of possible clinical side effects is limited. Detailed studies are therefore required and a prospective clinical study was designed to investigate acute changes in renal function following ESWL of renal stones.

## Patients and Methods

Seventeen patients, 10 women and 7 men (mean age 51.8 years; range 18–72) with stones in the renal pelvis and/or calices were studied. All had a total stone burden less than 2.5 cm in diameter. Patients

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with any sign of obstruction on intravenous urography (IVU) prior to treatment were excluded.

Two 24-h urine collections were sampled during the 2 days preceding treatment and 2 after, at 0–24 h and day 4–5. Blood tests were carried out on the same 2 days before ESWL, 1 immediately after, and then daily for 2 days. Clinical follow-up with 24-h urine samples and blood tests were performed in 13 patients 2 weeks and 3 months after treatment.

In 4 patients additional blood samples were obtained after immersion for 25 min in the water bath, immediately prior to ESWL, to evaluate the effects of premedication, sedation, intravenous infusion and water immersion (Table 1).

The patients were deprived of food and water from mid-night on the preceding day. Intravenous infusions of 1000 ml 5% glucose and 1000 ml normal saline were administered for 2 h during and after treatment and unlimited oral fluids were allowed thereafter. The patients were premedicated with pethidine 1 mg/kg. During treatment small doses of intravenous analgesics and sedatives were administered according to individual needs (mean 0.08 mg phentanyl and 1.82 mg benzodiazepine).

ESWL was performed by the modified Dornier HM3 lithotriptor (Graff *et al.*, 1988). The mean number of exposures was 2253 (range 1000–3000), delivered at 18–20 kV. The mean duration of water immersion was 23 min (range 15–20), the water temperature being constant at 37°C.

*Analytical methods.* Creatinine (µmol/1) in serum (mean normal value ± 1SD = 88.4 ± 12.6) and urine were determined by a rate-dependent modification of the Jaffe reaction using a creatinine analyser (Beckman model 2). All clearance values were corrected to 1.73 $m^2$ body surface. $\beta_2$-microglobulin in serum (µg/1) and urine (µg/24 h) were assayed by a commercial radioimmunoassay (RIA) kit (Pharmacia AB, Uppsala, Sweden). Urine was stored at pH > 6. The serum values in healthy controls were 2225 ± 787 µg/1 and the urinary excretion was 137 ± 66 µg/24 h. The within assay coefficient of variation was 5% in serum and 7.7% in urine. Urine volume (UV) was measured in ml/min. Urinary albumin excretion (µg/24 h) was determined by an RIA kit (Pharmacia AB, Uppsala, Sweden). The excretion in healthy controls was 4.0 ± 2.6 µg/24 h. The within assay coefficient of variation was 9%. Urine and serum osmolalities (m Osmol/kg) were determined by the freezing point depression method (Hermann Roebling Osmometer, Berlin, W. Germany). Urinary alkaline phosphatase (ALP) (units/mmol creatinine) was measured by photospectrometry using a commercial kit (Boehringer, Mannheim GmbH Diagnostica, W. Germany). The mean value in the reference material was 0.188 ± 0.077 units/mmol creatinine. The within assay coefficient of variation was 3.7%. Urinary NAG (units/µmol creatinine) was determined by the fluorometric method of Price *et al.* (1970) using methylumbelliferylglucosaminidine as substrate. The mean value in the reference material was 5.4 ± 2.3 units/µmol creatinine. The within assay coefficient of variation was 3%. PRA (nmol/1/h) was determined by radiommunoassay of angiotensin I before and after incubation of plasma samples according to Sundsfjord (1971). The normal range for ambulatory patients is 0.5–1.5 nmol/1/h; the within assay coefficient of variation for the method was 8%. Serum aldosterone (picomol/l) was measured by radioimmunoassay, using reagents from Diagnostic Product Cooperation (DPC). This radioimmunoassay employs $^{125}$I labelled aldosterone and antibody-coated tubes. The normal range for ambulatory patients is 70–450 picomol/l; the within assay coefficient of variation was 5%. Endogenous clearance of creatinine ($C_{Cr}$, ml/min) was used as index for GFR. Osmolal clearance ($C_{osmol}$, ml/min) and free water clearance ($C_{H_2O}$, ml/min) were calculated using conventional formulae.

**Table 1** Changes in Blood Variables in 4 Patients before and after Immersion in Water for 25 min prior to ESWL

| *Variable* | *Before immersion* *Mean ± SEM* | *After immersion* *Mean ± SEM* |
|---|---|---|
| Hct (%) | 0.45 ± 0.01 | 0.40 ± 0.01 |
| Osmolality (m Osmol/1) | 302 ± 0.8 | 301 ± 0.9 |
| Protein (g/1) | 75.2 ± 3.4 | 62.2 ± 1.4 |
| Albumin (g/1) | 46.0 ± 0.4 | 37.5 ± 1.0 |
| Na (mmol/l) | 143.5 ± 0.3 | 140 2 ± 0.9 |
| K (mmol/1) | 3.6 ± 0.5 | 4.4 ± 0.1 |
| PRA (nmol/l/h) | 1 1 ± 0.5 | 0.5 ± 0.3 |
| Aldosterone (picomol/1) | 316 5 ± 31.6 | 153.5 ± 10.7 |

Haemoglobin (Hb, g/dl), haematocrit (Hct, %), white blood cell count (WBC, $10^9$/l), red blood cell count (RBC, $10^{12}$/l), haptoglobin (g/l), serum uric acid (µmol/l), plasma protein (g/l), albumin (g/l), serum and urinary electrolytes (mmol/l) and serum lactic dehydrogenase (LD, U/l) were measured by conventional methods.

The mean of the measured values obtained before and after ESWL were calculated. The mean and standard error of the mean (SEM) are used for the presentation. The means of the values obtained before (control) and at each of the tests after ESWL were compared statistically by the 2-tailed Wilcoxon signed rank test.

## Results

Urine volume was increased from 1.2 ± 0.1 to 2.2 ± 0.7 ml/min 24 h after ESWL ($P < 0.001$). $C_{Cr}$ remained unchanged. As there was no alteration in $C_{osmol}$, $C_{H_2O}$ increased from −0.6 ± 0.1 to +0.4 ± 0.1 ml/min ($P < 0.01$) during the first 24 h (Table 2). Baseline values were obtained between 4–5 days and 2 weeks. S-creatinine did not change following ESWL (Table 3). The small reduction in S-urea and S-$\beta_2$-microglobulin after ESWL was probably secondary to haemodilution and increased plasma volume during treatment (Table 1). Increased plasma volume also probably accounted for the significant reduction in PRA and S-aldosterone.

Urinary exretion of proteins (albumin and $\beta_2$-microglobulin) increased significantly during the first 24 h after ESWL (Table 4). Urinary enzyme excretion (NAG and ALP) was also elevated. Pretreatment values were obtained on day 4–5.

S-LD increased from 352 ± 15.8 U/l before ESWL to 419 ± 15.3 U/l after ($P < 0.001$) and remained high 2 weeks after treatment ($P < 0.05$). At 3 months there was no significant change.

## Discussion

ESWL is now the major treatment for most stones in the upper urinary tract. The increasing tendency

**Table 2** Effects of ESWL on UV, $C_{Cr}$, $U_{osmol}$, $C_{osmol}$ and $C_{H_2O}$ (Mean ± SEM)

| | *Before ESWL* | *After ESWL* | | | |
|---|---|---|---|---|---|
| *Urine parameter* | | *0–24 h* | *Day 4–5* | *2 weeks* | *3 months* |
| UV (ml/min) | 1.2±0.1 | 2.2±0.7‡ | 1.6±0.2† | 1.4±0.1 | 1.1±0.1 |
| $C_{Cr}$ (ml/min) | 84±5 | 84±5 | 86±8 | 90±7 | 81±5 |
| $U_{osmol}$ (mosmol/kg) | 480±28 | 256±17‡ | 363±37† | 492±48 | 517±59 |
| $C_{osmol}$ (ml/min) | 1.8±0.1 | 1.8±0.1 | 1.8±0.2 | 2.1±0.2 | 1.6±0.1 |
| $C_{H_2O}$ (ml/min) | −0.6±0.1 | 0.4±0.1† | −0.2±0.2 | −0.8±0.2 | −0.6±0.1 |

†$P < 0.01$

‡$P < 0.001$.

**Table 3** Effects of ESWL on Renal Glomerular Function, PRA and Serum Aldosterone (Mean ± SEM)

| | *Before ESWL* | *After ESWL* | | | | |
|---|---|---|---|---|---|---|
| *Variable* | | *0 h* | *24 h* | *48 h* | *2 weeks* | *3 months* |
| S-creatinine (µmol/l) | 94±3 | 96±4 | 99±6 | 101±8 | 94±3 | 90±3 |
| S-urea (mmol/l) | 4.9±0.2 | 4.2±0.2† | 4.4±0.3* | 4.7±0.2 | 4.6±0.3 | 4.5±0.2 |
| S-$\beta$ microglobulin (µg/l) | 1648±93 | 1507±82 | 1612±85 | 1675±104 | 1670±116 | 1738±124 |
| PRA (nmol/l/h) | 1.2±0.4 | 0.7+0.2† | 1.0±0.3 | 1.5±0.5 | 1.5±0.8 | 1.5±0. |
| S-aldosterone (picomol/l) | 374±52 | 193±36† | 294±48 | 388±63 | 381±58 | 450±73 |

*$P < 0.05$.

†$P < 0.01$.

**Table 4** Effects of ESWL on Renal Protein and Enzyme Excretion (Mean ± SEM)

| *Urine parameter* | *Before ESWL* | *After ESWL* | | | |
|---|---|---|---|---|---|
| | | *0–24 h* | *Day 4–5* | *2 weeks* | *3 months* |
| Albumin (µg/min) | 60±22 | 286±83* | 44±18 | 26±12 | 26±16 |
| $\beta_2$ microglobulin (µg/24 h) | 215±38 | 599±234† | 372±103 | 219±51 | 211±44 |
| NAG (units/µmol creatinine) | 5.9±0.6 | 15.1±4.2* | 7.8±1.7 | 6.0±1.0 | 7.0±1.8 |
| ALP (units/mmol creatinine) | 0.4±0.1 | 1.7±1.1‡ | 0.5±0.2 | 0.4±0.1 | 0.4±0.1 |

*$P < 0.001$.

†$P < 0.01$.

‡$P < 0.05$.

to repeat ESWL sessions for the treatment of large and hard stones calls for knowledge of any side effects of clinical importance.

GFR did not change following ESWL in this study, based on measurements of $C_{Cr}$, S-creatinine and S-$\beta_2$-microglobulin. The results are in accordance with our animal data (Karlsen *et al.*, 1990b), studies in minipigs (Evan *et al.*, 1989) and some clinical series (Kishimoto *et al.*, 1986; Lingeman *et al.*, 1986; Gilbert *et al.*, 1988). Others report increased levels of serum creatinine (Pettersson, 1989) and reduced GFR in patients (Bomanji *et al.*, 1987) and rabbits (Gunasekaran *et al.*, 1989) after ESWL.

Graded water immersion in humans gradually reduces ADH activity (Norsk *et al.*, 1986), leading to a diuresis and increment in $C_{H_2O}$ and osmotic excretion. The significant increases in urine volume, Uosomol and $C_{H_2O}$ 0–24 h after ESWL (Table 2) are probably secondary to this effect.

Urinary excretion of albumin and $\beta_2$-microglobulin was significantly increased 0–24 h following ESWL. The excretion of albumin returned to normal by day 4–5, supporting the data of other investigators (Wilbert *et al.*, 1988). In one study, however, albuminuria persisted for 3 months (Gilbert *et al.*, 1988). The increment in albumin excretion is partially due to the haematuria which occurs after treatment. However, haematuria cannot account for the increased urinary excretion of $\beta_2$-microglobulin since nearly all of the $\beta_2$-microglobulin filtered by the glomerulus is normally reabsorbed by the proximal tubule. Tubular dysfunction with incomplete reabsorption of albumin and $\beta_2$-microglobulin is a possible explanation. Altered glomerular membrane permeability as a direct result of the shock waves could cause leakage of albumin. Electron microscopy revealed breaks in Bowman's capsule caused by extracorporeal shock waves in canine kidneys (Karlsen *et al.*, 1990a and b).

The urinary excretion of the lysosomal enzyme NAG and the brush border enzyme ALP, both indicators of proximal tubular function, was significantly increased 0–24 h after ESWL (Table 4). Although some authors found no significant rise in urinary NAG after ESWL (Ruiz Marcellan and Ibarz Servio, 1986; Trinchieri *et al.*, 1988), our data did reveal evidence of transient tubular damage on the basis of increased enzymuria (Kishimoto *et al.*, 1986; Assimos *et al.*, 1987) and excretion of $\beta_2$-microglobulin (Wilbert *et al.*, 1988).

In a small percentage of patients a possible relationship has been described between ESWL and the development of hypertension (Williams *et al.*, 1987). To the best of our knowledge, the present clinical study is the first to investigate the acute effects of ESWL on PRA and serum aldosterone. Although our studies in dogs could suggest a triggering of the renin-angiotensin system following renal exposure to extracorporeal shock waves (Karlsen *et al.*, 1990b), PRA and serum aldosterone were not influenced by ESWL in this clinical study. The significant decrease in these parameters immediately after treatment (Table 3) was attributable to an increment in plasma volume secondary to redistribution of blood volume into central vessels during water immersion (Norsk *et al.*, 1986) and expansion of the extracellular volume (ECV) secondary to intravenous fluid load.

Immersion in water has marked effects on plasma volume and several hormones regulating renal function (Norsk *et al.*, 1986). Our results (Table 1) indicate that immersion also influences these parameters during ESWL. The significant reduction in Hb, Hct, haptoglobin, WBC and RBC may be explained by haemodilution alone, as reported by Gilbert *et al.* (1988).

The significant increase in serum LD is confirmed by other authors (Kishimoto *et al.*, 1986; Ruiz Marcellan and Ibarz Servio, 1986; Petterson, 1989) and probably reflects the effects on all tissues traversed by the shock waves and may also indicate haemolysis.

The changes in renal function observed after ESWL treatment in this study were moderate. Some of the effects were not specific to ESWL but attributable to haemodilution and water immersion alone. GFR was unaltered. Tubular function appeared more vulnerable, with significant changes in urinary excretion of $\beta_2$-microglobulin, NAG and ALP. Comparing these factors in patients receiving less than 2000 exposures ($n = 7$) with those exposed to 2000 or more ($n = 10$) revealed no significant difference. Since all of these changes returned to normal after 4 or 5 days, it was concluded that ESWL is a safe procedure as far as renal function is concerned.

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# Eicosanoid Synthesis in the Isolated Human Renal Pelvis, Ureter and Bladder

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Summary—Prostaglandin synthetase inhibitors are used for the treatment of ureteric colic. However, there is controversy regarding the mechanism of action of these drugs. In this study, differential prostaglandin synthesis in the human renal pelvis, ureter and bladder was measured using specific radioimmunoassays and gas chromatography/mass spectrometry. There was a significant quantitative predominance of the smooth muscle constrictor eicosanoids, $PGF_2\alpha$ and $TXA_2$ over the dilatory $PGE_2$ in tissue from all sites—renal pelvis, ureter and bladder.

The results indicate that prostaglandins play a direct role in smooth muscle activity of the upper urinary tract and the inhibition of this activity with indomethacin indicates a further mode of its action in pain relief in ureteric colic.

The prostaglandins, thromboxanes and leucotrienes belong to a large family of metabolites of arachidonic acid and have multiple functions (Debruyne, 1986).

Prostaglandins have been shown to modulate the tension of smooth muscle in the urinary bladder and urethra (Bultitude *et al.*, 1976; Andersson *et al.*, 1977). In addition, they are used clinically to stimulate detrusor muscle activity (Bultitude *et al.*, 1976; Delaere *et al.*, 1981; Debruyne, 1986).

Prostaglandins influence renal function as well as having a direct effect on the renal pelvis and ureter. *In vitro* studies using smooth muscle from the upper urinary tract have demonstrated the contractile action of prostaglandins $F_2\alpha$ and $E_2$ upon ureteric and pelvic smooth muscle (Thulesius and Angelo Khattar, 1985; Cole *et al.*, 1988). Furthermore, indomethacin and other prostaglandin synthetase inhibitors have been reported to have an inhibitory effect upon contraction of smooth muscle obtained from the upper urinary tract (Angelo Khattar *et al.*, 1985; Lundstam *et al.*, 1985; Thulesius and Angelo Khattar, 1985; Cole *et al.*, 1988). These drugs are effective in providing pain relief in ureteric colic (Holmlund and Sjödin, 1978; Marsala, 1980; Lundstam *et al.*, 1982; Cole *et al.*, 1989). However, their mechanisms of action are not fully understood as the factors provoking ureteric colic are complex and inter-relate in a complicated manner. Indomethacin has been shown to block the initial increase in renal blood flow in response to acute ureteric obstruction, thereby tending to reduce the renal pelvic pressure (Allen *et al.*, 1978).

Locally secreted prostaglandins may also produce oedema around the obstructing stone, preventing its progression and increasing ureteric obstruction (Sjödin, 1981). Inhibition of this local prostaglandin synthesis may reduce oedema and to some extent diminish the degree of obstruction. In addition, the reduced contractility of ureteric and pelvic smooth muscle due to prostaglandin synthetase inhibitors has already been mentioned as a further factor in promoting pain relief.

Several workers (Abrams *et al.*, 1979; Brown *et al.*, 1980; Jeremy *et al.*, 1987) have demonstrated the ability of the bladder to synthesise various eicosanoids. The present study was designed to analyse the eicosanoid content of the human ureter, renal pelvis and bladder. The capacity of these tissues to synthesise eicosanoids has also been

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investigated. Eicosanoid synthesis was shown to be inhibited by prostaglandin synthetase inhibitors.

## Materials and Methods

Tissue from the renal pelvis and ureter (approximately 3 × 10 mm, weighing 20–60 mg) was obtained from kidneys removed because of renal carcinoma in one pole. Small strips of the bladder dome were excised for analysis in patients undergoing ureteric reimplantation.

Two groups of experiments were performed:

1. The tissue content of eicosanoids was determined with radioimmunoassay;
2. The capacity of tissue to synthesise eicosanoids was measured by radioimmunoassay and gas chromatography/mass spectrometry. Details of this technique are described by Leis *et al.* (1987).

### *Tissue content of eicosanoids*

After removal of fat and traces of blood, the strips of tissue were washed in a Krebs-Henseleit solution consisting of 113.8 mmol/l NaCl, 22 mmol/l $NaHCO_3$, 4.7 mmol/l KCl, 1.2 mmol/l $KH_2PO_4$, 1.1 mmol/l $MgSo_4$, $\times 7H_2O$, 2.5 mmol/l $CaCl_2 \times 2H_2O$ and 5.5 mmol/l glucose, and stored at −70°C prior to eicosanoid analysis. The samples were then homogenised. The homogenates were acidified to pH 3.5–4.0, suspended in 5–6 ml ethyl acetate, mixed and centrifuged. The extraction in ethyl acetate was performed twice. The supernatants of the ethyl acetate fractions were then reduced to dryness under nitrogen, resuspended, and the prostaglandins $E_2$, $F_2\alpha$, thromboxane $TXB_2$ and 6-keto $PGF_1\alpha$ (the stable products of thromboxane $TXA_2$ and prostacyclin $PGI_2$ respectively) were determined by specific radioimmunoassays (Amersham Buchler, Braunschweig, Germany).

Eicosanoid content is expressed as nanogram per gram wet tissue (mean ± standard error of the mean). The eicosanoid content of the urinary tract was compared with that of healthy strips of human vein analysed in the same manner.

### *Eicosanoid synthesis*

The strips of urinary tract tissue were pinned on a cork board; at least 8 discs of approximately the same size (3 × 10 mm) were removed and each placed in 1 ml Krebs-Henseleit medium pre-gassed with 95% $O_2$, 5% $CO_2$. The samples were then incubated at 37°C in a shaking water bath. Two of the incubated discs were incubated with the control medium alone. To the other discs various concentrations of indomethacin (10 µl containing increasing amounts: 10 mg/l, 50 mg/l, 100 mg/l) were added and incubated for 30 min. After incubation the reaction was stopped: ethyl acetate was added to the solutions to be analysed by specific radioimmunoassay and formic acid was added to those undergoing gas chromatography/mass spectrometry. The tubes were centrifuged for 5 min and the supernatants removed for eicosanoid estimation.

The tissue was always weighed, either wet (after being blotted between filter paper) or dry (after desiccation). Eicosanoid production was expressed in nano- or picogram per 10 mg wet or dry tissue (mean ± standard error of the mean).

Statistical differences were evaluated by the Wilcoxon test.

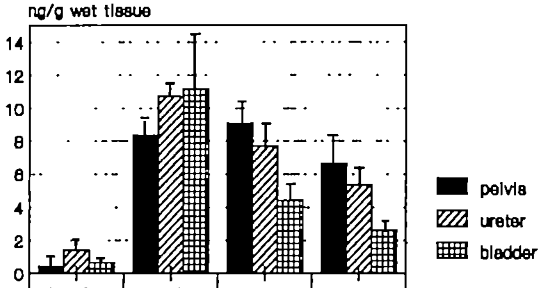
## Results

### *1. Tissue content of eicosanoids (Fig. 1)*

In the bladder and also in the upper urinary tract (ureter, renal pelvis), prostaglandin $E_2$ and $F_2\alpha$, prostacyclin and thromboxane $A_2$ were found in small quantities, maximally 11 ng per gram wet tissue. The concentration of $PGE_2$ was much lower than those of the other eicosanoids. The tissue content of eicosanoids in healthy veins was considerably greater than that found in the urinary tract.

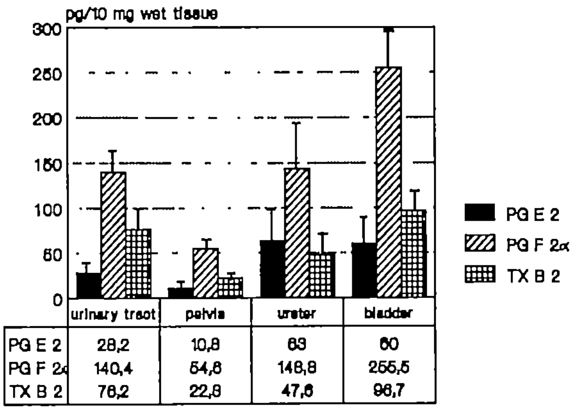
### *2. Eicosanoid synthesis*

*(a) Radioimmunoassays.* Tissue from the human renal pelvis, ureter and bladder was shown to release $PGF_2\alpha$, $PGE_2$ and $TXB_2$. In all strips, $PGF_2\alpha$ was released in the highest quantity (140.4 ±



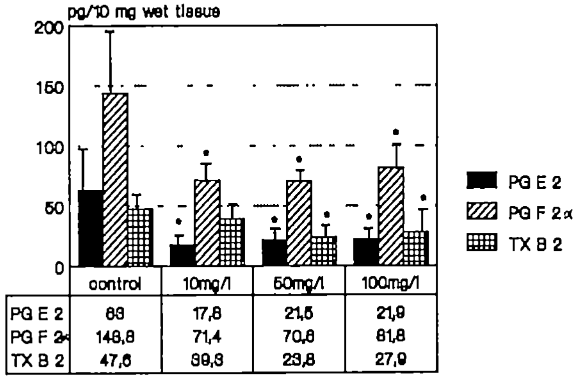
| | PG E 2 | PG F 2α | TX B 2 | 6-k-PG F1α |
|---|---|---|---|---|
| pelvis | 0,48 | 8,83 | 9,06 | 6,62 |
| ureter | 1,42 | 10,74 | 7,69 | 5,85 |
| bladder | 0,65 | 11,19 | 4,41 | 2,62 |
| vein | 8,67 | 30,22 | 67,48 | 45,09 |

**Fig. 1** Eicosanoid tissue content (prostaglandins $E_2$, $F_2\alpha$, thromboxane $TXA_2$ ($TXB_2$) and prostacyclin (6-keto $PGF_1\alpha$) of human renal pelvis (n = 7), ureter (n = 7), bladder (n = 5) and healthy veins (n = 13) determined by radioimmunoassay.



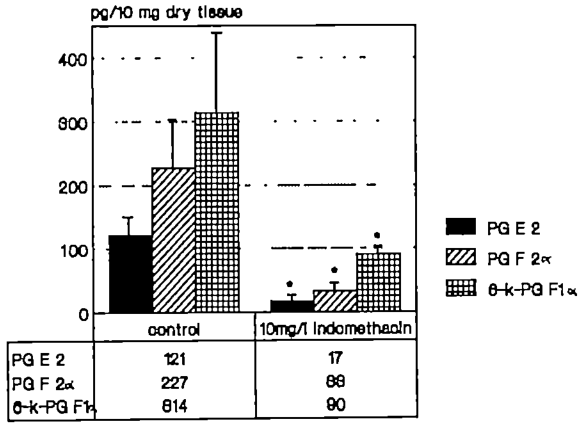
| | urinary tract | pelvis | ureter | bladder |
|---|---|---|---|---|
| PG E 2 | 28,2 | 10,8 | 63 | 60 |
| PG F 2α | 140,4 | 54,8 | 146,8 | 255,5 |
| TX B 2 | 76,2 | 22,8 | 47,6 | 96,7 |

**Fig. 2** Eicosanoid release of human tract (renal pelvis n = 7, ureter n = 7 and bladder n = 5 determined by radioimmunoassay).



| | control | 10mg/l | 50mg/l | 100mg/l |
|---|---|---|---|---|
| PG E 2 | 63 | 17,8 | 21,5 | 21,9 |
| PG F 2α | 146,8 | 71,4 | 70,6 | 81,8 |
| TX B 2 | 47,6 | 39,3 | 23,8 | 27,9 |

**Fig. 3** Eicosanoid release of human ureter (n = 7) before and 30 min after incubation with various amounts of indomethacin (using radioimmunoassay). *$P<0.05$ control vs groups with indomethacin.



| | control | 10mg/l Indomethacin |
|---|---|---|
| PG E 2 | 121 | 17 |
| PG F 2α | 227 | 38 |
| 6-k-PG F1α | 314 | 90 |

**Fig. 4** Eicosanoid release of human renal pelvis (n = 7) before and 30 min after incubation with 10 mg/l indomethacin (using gas chromatography/mass spectrometry). *$P<0.05$ control vs indomethacin.

31.4 pg/10 mg wet tissue); $TXB_2$ production was smaller (76.2 ± 23.7 pg/10 mg wet tissue) and $PGE_2$ production was the least (28.2 ± 15 pg/10 mg wet tissue) (Fig. 2).

After incubation with different amounts of indomethacin the production of $PGF_2\alpha$ and $PGE_2$ of the ureter was significantly reduced ($P<0.05$), whereas this effect was found with $TXB_2$ only after larger indomethacin concentrations (Fig. 3).

*(b) Gas chromatography/mass spectrometry (Fig. 4)*. The $PGF_2\alpha$ production of human renal pelvis also showed a quantitative predominance, while $PGE_2$ was released in lowest quantities. After incubation for 30 min with only 10 mg/l indomethacin there was a significant decrease in prostaglandin synthesis *in vitro* ($P<0.05$).

## Discussion

The present study shows that the human upper urinary tract, the renal pelvis and the ureter are able to synthesise eicosanoids, as has been found in the bladder of man (Abrams *et al.*, 1979; Jeremy *et al.*, 1987) and of rabbit (Brown *et al.*, 1980). These results give credance to the study of Al-Ugaily *et al.* (1986), who suggested that the large number of lipophilic granules seen in the vicinity of smooth muscle cells on electron microscopy could serve as prostaglandin precursors and reinforce the results of Thulesius (1987), who found eicosanoid release from sheep ureter into an organ bath.

The measured amounts of the eicosanoids released by the urinary tract in this study (28–256 pg/mg tissue) are lower than those measured by Jeremy *et al.* (1987) from bladder (0.9–58 ng/mg tissue). However, both techniques used for estimating eicosanoid synthesis in this study—radioimmunoassay and gas chromatography/mass-spectrometry—gave comparable results for the ureter and the renal pelvis. Nevertheless, the validity of the present study is limited by the small number of samples and by the variation in the relative amounts of different eicosanoids released. It may be difficult to extrapolate these results to an *in vivo* situation, since the trauma during tissue preparation is known to be a stimulus for eicosanoid release. In addition, it is known that variations in the physiological environment, such as pH, may alter eicosanoid synthesis. Furthermore, prostaglandin synthesis is altered in a variety of pathological conditions (Jeremy *et al.*, 1984, 1985, 1987). Since prostaglandins and thromboxanes are also produced by other tissues, *e.g.* fat or blood, great care must be taken to remove these tissues (Abrams *et al.*, 1979).

The low level of eicosanoid tissue content in the urinary tract (with a maximum of 11 ng/g wet tissue) is compatible with the idea that prostaglandins and thromboxanes are not stored, but are synthesised according to need (Debruyne, 1986).

The tissue content of prostaglandins in bladder was less than that measured by Abrams *et al.* (1979). Of special interest is the large difference between the eicosanoid content found in veins compared to that in the urinary tract. The various functions and different anatomical structures may provide an explanation for this finding (Kuschinsky and Lüllmann, 1987). It is known that large quantities of prostacyclin ($PGI_2$) are released by vascular tissue (Bunting *et al.*, 1976; Moncada, 1982), but extravascular production of $PGI_2$ and $TXA_2$ has also been found in other tissues, for instance in the urinary tract (Thulesius *et al.*, 1987).

Experiments in isolated animal and human ureteric and pelvic strips have shown that exogenous prostaglandins can alter the contractile response of these smooth muscles. In addition, contractile activity could be inhibited by indomethacin and other prostaglandin synthetase inhibitors (Lundstam *et al.*, 1985; Thulesius and Angelo Khattar, 1985; Cole *et al.*, 1988). Furthermore, Thulesius *et al.* (1987) demonstrated that the release of prostanoids from sheep ureter into an organ bath could be inhibited by indomethacin. These results provide evidence that prostaglandin synthetase inhibitors may directly change the smooth muscle activity of the upper urinary tract, a mechanism which might explain the pain-relieving qualities of these drugs during ureteric colic. While opioids especially seem to act centrally, indomethacin has a variety of actions upon the urinary tract itself. It appears to block the normal physiological renal response to acute ureteric obstruction leading to a fall in the renal pelvic pressure (Holmlund and Sjödin, 1978; Lundstam *et al.*, 1982). Decreased oedema around the obstructing stone may be a further explanation for the effect of indomethacin (Sjödin, 1981).

Indomethacin inhibits both the prostaglandins which dilate ($PGI_2$-stable metabolite 6-keto-$PGF_{2}\alpha$ and $PGE_2$) and constrict tissue (TXA-stable metabolite $TXB_2$ and $PGF_{2}\alpha$). Since good clinical results have been reported for indomethacin in ureteric colic (Marsala, 1980; Holmlund *et al.*, 1982; Flannigan *et al.*, 1983; Cole *et al.*, 1989), the inhibition of the prostaglandins, which cause constriction, must prevail over the inhibition of the dilatatory prostaglandins.

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# Intrarenal Pressure following Pyeloplasty or Percutaneous Surgery

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Summary—In a study of 37 patients it was shown that recording the intrapelvic pressure is a safe and reliable means of judging the best time to remove a nephrostomy tube. No post-operative complications were encountered and the procedure has the added advantage of avoiding the use of X-rays.

The criteria that are generally considered before removing a nephrostomy tube following pyeloplasty or a percutaneous procedure are empirical. Such criteria are neither objective nor reliable. The aim of this study was to establish whether intrapelvic pressure recording was a better means of deciding when to remove a nephrostomy tube (Lupton *et al.*, 1979). A nephrostogram was also performed in each case.

## Patients and Methods

The study group included 37 patients. Intrarenal pressures were measured in 8 patients after pyeloplasty and in 22 patients after percutaneous surgery. At the same time, all patients were checked by nephrostography.

A nephrostomy tube was connected to a pressure transducer while bladder pressures were measured via a 14F urethral catheter. A combination of saline solution and methylene blue was instilled by a perfusion pump at a flow rate of 10 ml/min into the kidney via the nephrostomy tube (Whitaker *et al.*, 1979, 1981) and pressures were recorded. Pressures exceeding 22 cm $H_2O$ were judged to be obstructive, 15 to 22 cm $H_2O$ were equivocal and pressures lower than 15 cm $H_2O$ were considered normal (Lupton *et al.*, 1985). The resistance of the infusion set was 2 cm $H_2O$ and this was subtracted from the intrarenal pressure. By measuring the intrarenal pressure during the steady flow of methylene blue through the urethral catheter, an unnecessary X-ray procedure was avoided.

## Results

In 8 patients intrarenal pressure was normal on the seventh day following pyeloplasty. The tubes were removed and there were no post-operative complications. In 16 patients intrarenal pressure was lower than 15 cm $H_2O$ 2 days after percutaneous surgery and the nephrostogram was normal. The nephrostomy tubes were removed and there were no post-operative complications.

In 4 patients with a horseshoe kidney and hydronephrosis, pressures were high and the nephrostomy tube was retained for some time. Bilateral percutaneous nephrostomy was performed on 2 patients who developed a urinary tract obstruction due to carcinoma of the cervix. Nephrostography was performed 1 month later and demonstrated drainage; the intrarenal pressures were high, however, and the nephrostomy tubes were retained.

A Cohen ureteric reimplantation was performed on 1 patient whose kidney was decompressed 30 days before operation with a percutaneous nephrostomy. No flow of contrast could be demonstrated on the tenth day, when intrarenal pressures were high, but was seen after 20 to 30 days, when intrarenal pressures were normal. The tube was

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then removed and the patient made an uneventful recovery.

## Discussion

This study involved modifying the Whitaker test to suit our needs and, by waiting until pressures were normal before removing the nephrostomy tube, post-operative complications were avoided. The use of methylene blue as described, together with the pressure measurements, also meant that the patient was not exposed to unnecessary X-ray radiation.

These studies have enabled us to make more informed decisions on the timing of nephrostomy tube removal and so prevented problems commonly associated with its premature removal.

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# Misdiagnosed Papillary Renal Adenocarcinoma

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Summary—We present 3 patients with papillary renal adenocarcinoma who were initially misdiagnosed owing to unusual clinical presentation. We suggest that if these presentations are borne in mind, pre-operative detection of this uncommon condition should be possible more often than is now the case.

Papillary renal adenocarcinoma (PRA) is an uncommon variant of renal carcinoma and may be detected incidentally following spontaneous rupture of the kidney or after minimal flank trauma. Although the various clinical presentations associated with PRA could be seen in our patients (Table 1), the diagnoses were not made pre-operatively. A wider appreciation of these unusual characteristics should help in making a full diagnosis at an earlier stage in future.

**Table 1** Characteristics of Papillary Renal Adenocarcinoma

| |
|---|
| Hypovascularity |
| Necrotic and cystic consistency |
| Slow growing and rarely metastatic |
| Renal mass known prior to operation |

## Patients and Methods

The 3 patients underwent surgery in other departments because of their unusual presentations. Two received emergency surgery and the third had an elective operation. Because of the benign appearance, partial nephrectomy was performed on 2 patients. One of these required a second operation after the histology report was received and metastases were found in the para-aortic lymph nodes. The second patient refused further surgery and the third, who had undergone simple nephrectomy, received post-operative irradiation. Follow-up was carried out by abdominal CT and no tumour recurrence was found.

Details of the patients are shown in Table 2.

**Table 2** Details of Patients

| *Patient no* | *Age/Sex (years)* | *Department* | *Clinical presentation* |
|---|---|---|---|
| 1 | 21/M | Urology | Abdominal and flank pain with massive haematuria following mild flank trauma |
| 2 | 67/M | Surgery | Suspected acute appendicitis |
| 3 | 72/F | Gynaecology | Abdominal calcified mass revealed during pre-operative preparation for hysterectomy |

## Case Reports

*Case 1.* This male patient received a blow in the right flank during a game of basket ball. He complained of abdominal and flank pain accompanied by massive haematuria. Intravenous urography (Fig. 1) showed compression of the right upper calix without extravasation. His condition deteriorated and blood and fluid support were required. Plain X-ray (Fig. 2) revealed left deviation of the gut. Since a large haematoma and acute bleeding were a possibility, exploration of the right kidney was performed. The retroperitoneum and Gerota's fascia were found to be occupied by necrotic and spongy tissue originating from rupture of a capsulated mass in the upper pole of the kidney (Fig. 3). The mass was easily enucleated and the remaining part of the kidney was not examined. Re-exploration was necessary, however, because the pathology finding was clear cell carcinoma (Fig. 4). In the second operation, metastasis was found in the para-aortic lymph nodes. No adjuvant therapy was given.

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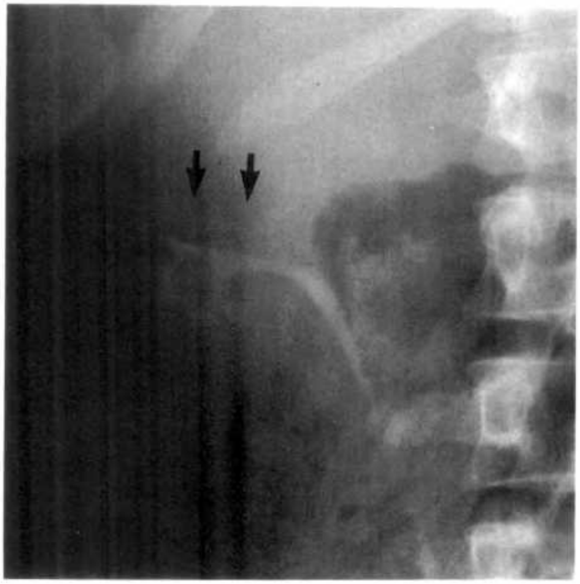

**Fig. 1** Intravenous urography showing compression of right upper calix and distortion of the calices.

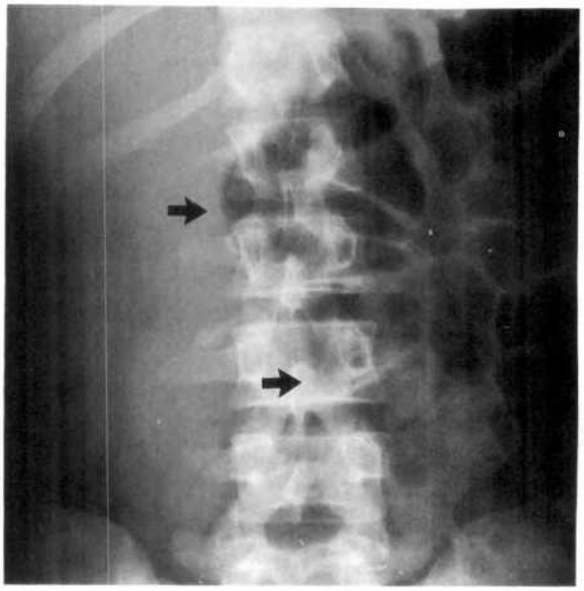

**Fig. 2** Plain X-ray showing deviation of gut to left.

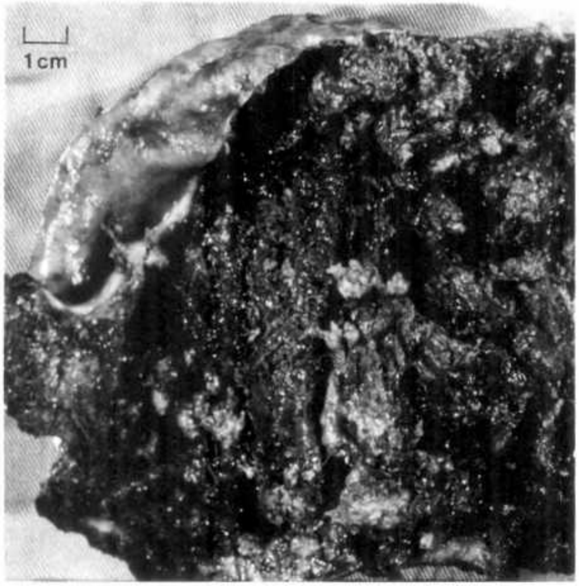

**Fig. 3** Cut surface of tumour showing large areas of necrosis, haemorrhage and softening.

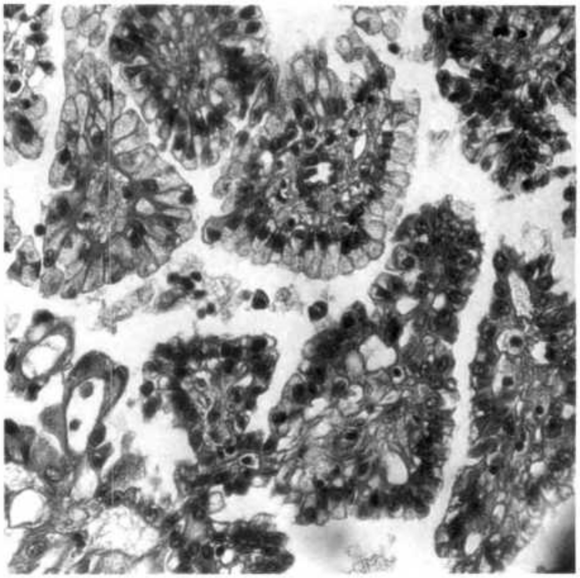

**Fig. 4** Papillary pattern of tumour showing clear cells with round or polygonal shape and abundant clear cytoplasm. (H and E × 100).

*Case 2.* This patient was well until the day before admission, when he experienced loss of appetite and a bitter taste in the mouth. On admission he complained of diffuse abdominal pain and physical examination revealed signs of acute appendicitis. Laparotomy revealed a normal appendix, cholelithiasis and a haematoma in the inferior mesocolon, probably of retroperitoneal origin. Exploration revealed a huge haematoma extending over the whole of the retroperitoneal area and this accounted for the diffuse abdominal pain and rebound tenderness. The haematoma originated from a perforated tumour of the right kidney. Simple nephrectomy was performed. The histology finding was papillary adenocarcinoma of the kidney and he received post-operative irradiation.

*Case 3.* This patient, an obese woman, had been prepared for abdominal hysterectomy for endometrial carcinoma. Pre-operative intravenous urography showed a calcified abdominal mass near the lower pole of the right kidney (Fig. 5) which was interpreted as teratoma or echinococcus. The mass was explored during the gynaecological operation and was found to be a tumour of the right kidney. The tumour was encapsulated and easily enucleated. The remaining kidney appeared normal. The histology finding was clear cell carcinoma. She refused a second operation and received no further treatment.

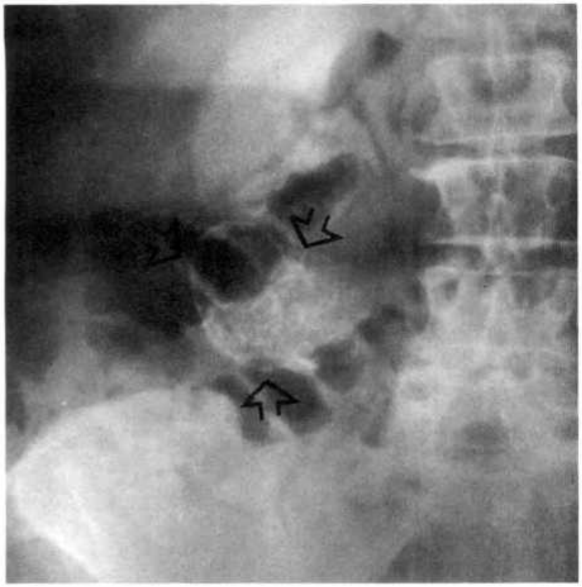

**Fig. 5** Irregular calcified abdominal mass near lower pole of right kidney.

## Results

Post-operative irradiation was given to only 1 patient and the others received no adjuvant therapy. The histological finding of PRA was unequivocal in 2 patients and the third had clear cell carcinoma of the kidney. Because of the calcification and uneventful follow-up after 3 years, we presumed the tumour to be of papillary pattern, and this was later confirmed (Fig. 6). No metastases were found in any of the 3 patients on abdominal CT 3 years post-operatively (Fig. 7).

## Discussion

PRA was a neglected entity until Mancilla-Jimenez *et al.* (1976) analysed its characteristics and compared it with non-papillary renal tumours (Table 3). Before then, studies of PRA had concentrated solely on hypovascularisation of the tumour (Melicow and Becker, 1967). Hand and Broders (1932) thought it had a favourable prognosis but presented no statistical data in support of this. Mancilla-Jimenez *et al.* (1976) emphasised the connection between pathological morphology of the tumour cells and prognosis of the disease and also found a high incidence of tumour calcification in PRA (32%) compared with the 10% found in all other types of renal carcinoma (Daniels *et al.*, 1972).

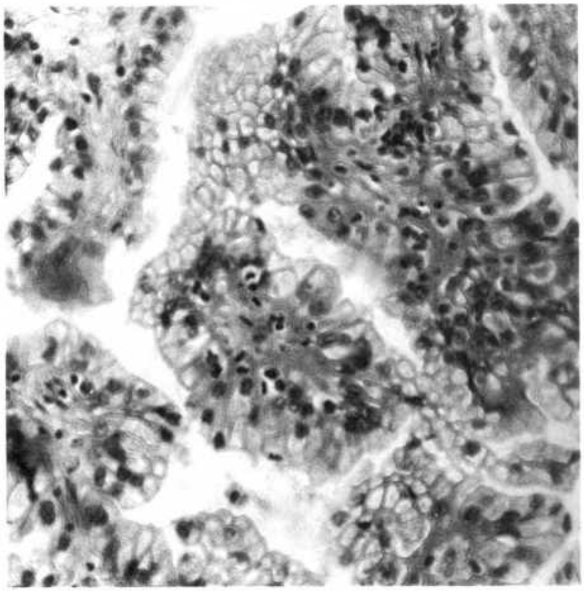

**Fig. 6** Renal carcinoma, papillary pattern, clear cell type. (H and E × 100).

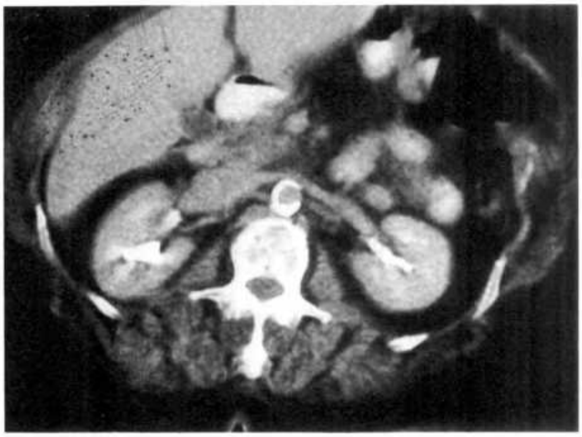

**Fig. 7** Patient no. 3: CT 3 years after partial nephrectomy.

Tumour necrosis was found in 70% of patients with PRA. Daniels *et al.* (1972) realised that the more necrotic the tissue the less aggressive the

**Table 3** Radiological, Pathological and Prognostic Factors in 224 Patients with Papillary and Non-papillary Renal Carcinoma (Manillo-Jimenez *et al.*, 1976)

| | *Papillary* | *Non-papillary* |
|---|---|---|
| No of patients | 34 | 190 |
| Hypovascularity on Angiography | 17/17 | 15/89 |
| Cystic necrosis (%) | 70 | 17 |
| Macrophage infiltration (%) | 59 | 6 |
| Pathology stage (%) | | |
| I | 85 | 42 |
| III | 12 | 42 |
| IV | 0 | 3.7 |
| Survival (%) | | |
| 5 years | 84 | 52 |
| Median (years) | 13 | 6 |

tumour, since arteries supplying the tumour were more sclerosed, narrower and thus prevented the formation of metastases. Several authors (Boczko *et al.*, 1979; Krieger *et al.*, 1979; Tsung and Lin, 1983) have tried to establish a connection between hypovascularity, necrosis, calcification and chronicity with the less aggressive pattern of PRA. Folkman (1976) suggested that it lacked the tumour angiogenesis factor (TAF), which prevented potential metastasis.

Because of its good prognosis, PRA is often asymptomatic for many years and some patients have been aware of a renal mass before its inadvertent clinical discovery.

We have also found that PRA is a possibility in cases of spontaneous tumour rupture as described by Mukamel *et al.* (1979) and Bagley *et al.* (1982). In cases of acute abdominal pain due to retroperitoneal haemorrhage without trauma, PRA may be responsible. This was the case in our second patient and has been reported by Uson (1959) and Bagley *et al.* (1982).

We consider that spontaneous rupture or traumatic haemorrhage of PRA is due to the soft consistency of this mostly necrotic, cystic tumour. The treatment of choice is nephrectomy. The debate centres on whether this should be a radical or a simple nephrectomy. In our first patient, we found metastasis only after lymph node dissection during the second operation. Because of the slow growing pattern of PRA, some surgeons prefer a conservative partial nephrectomy and periodically check the patients' progress by abdominal CT.

In conclusion, we believe that PRA should be suspected in certain specific situations. These include the presence of a hypovascular renal tumour revealed during renal angiography, a history of known renal mass, severe abdominal pain of unknown origin or massive haematuria following mild flank trauma.

## Acknowledgements

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# Computer Applications in a Urology Department

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Summary—An integrated approach to computerising the urology department has been implemented, using a XENIX multi-user system, with 6 terminals. Standard discharge letters, patient databases and urodynamic reporting programs are the main features. In addition, there are programs for patient history-taking and urodynamics on personal computers not linked at present to the main system.

The urology department at the Southern General Hospital has been using computer technology for many years now. The first computers to be used were Apple 2 machines which were used for word processing and related functions. Since then we have computerised our urodynamic data acquisition (Eadie *et al.*, 1986). This has expedited reporting of these tests to the extent that a 3-colour report is generated for analysis within minutes of the data being obtained. More recently a computer history-taking program has been developed (Glen *et al.*, 1989) which is designed to acquire a urological and general history from a patient and make suggestions for initial management. This has been in use for some 2 years now, with over 600 patients using the system. Few problems have been encountered with this program and we now have one of the shortest waiting times for first clinic appointments in the city. Recently an Apricot multi-user multi-tasking machine has been installed, running the Xenix operating system. We have created a set of programs and databases which have increased office efficiency and enhanced the quality of communications from the department to general practitioners and referring consultants.

## Materials and Methods

### *Multi-user system*

The multi-user computer is an Apricot Xen - i 386 with 100 MByte hard disk. It has the Xenix operating system and we have the Lyrix word processing and Foxbase database applications packages. The system has space for up to 12 users, although only 6 are in use at the moment. It services the secretaries, house officers, urodynamic specialists and physicist. This system has databases for patients, General Practitioners and drugs with instant recall of patient and referring doctor's details, including medication at the time of discharge. The programs facilitate surgical and management audit. We have written software permitting flexible generation of standard letters for discharge from the ward, attendance at outpatient clinics and urodynamic reporting. All of these applications are menu driven and friendly, and can be used by relatively inexperienced operators. All password holders have access to common databases, thus reducing the entry of duplicate details. With simple modifications the main programs could be used by most hospital departments. The multi-user applications are all running in Foxbase, which is very similar to DBASE3 plus, probably the commonest database in the world. By using common databases and mixing word processing and database applications, communication and efficiency are maximised. The features of the system are summarised in the Table. Urodynamics and computer history-taking require computing power at the terminal and are therefore implemented on personal computers, independent of the Xenix cluster.

### *Resident's discharge letter*

This application was written to replace the standard hospital form filled out by the urological residents.

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Read at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

**Table** Summary of Features of the Multi-user System

1. Key data on every in-patient are stored in a database.
2. Resident's discharge letters from the ward are now printed, with drugs selected from a database of standard doses.
3. Consultant's formal letters of discharge have access to the data input by the resident.
4. Doctors reporting urodynamics have access to a standard reporting format, which eliminates dictation and typing and also acts as an aid to reporting.

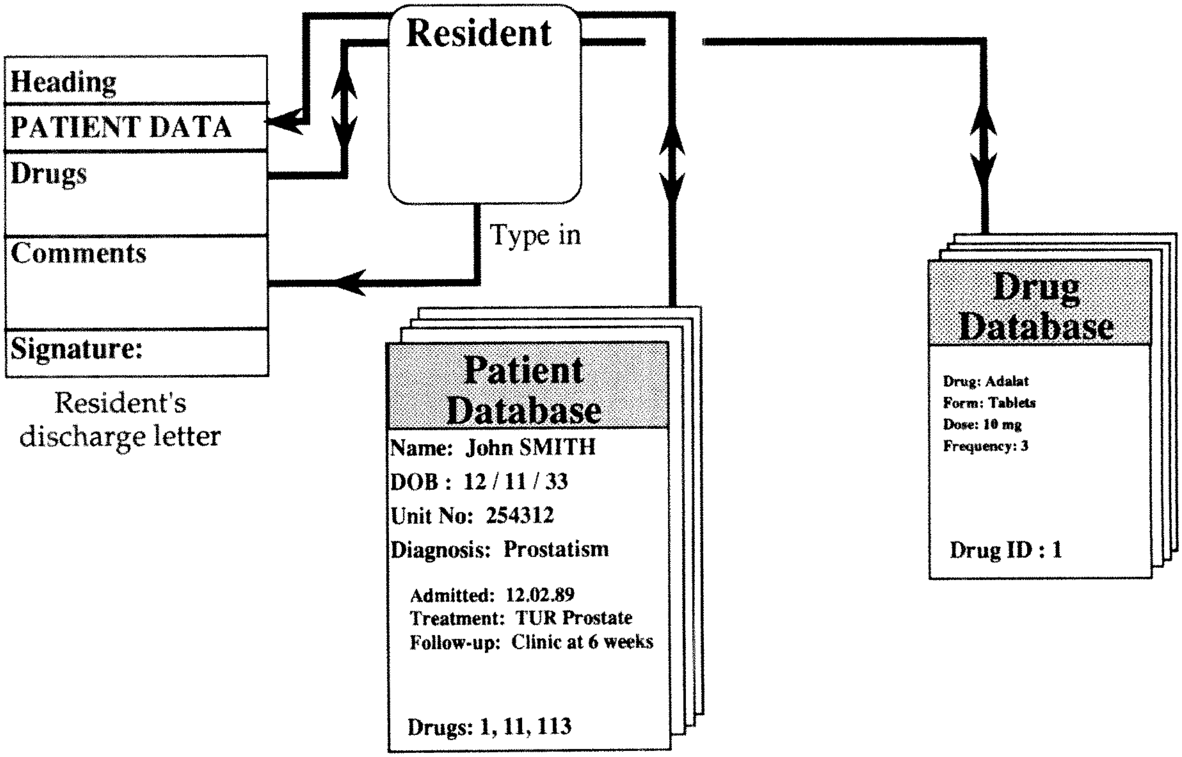
The form was handwritten and involved 3 carbon copies which were often difficult to read. The process followed by the resident is shown in Figure 1. The resident has access to a database of drug prescriptions, and the master patient database, using the data from these, adding typed diagnosis, treatment and comments to produce a letter. The process uses menu driven programs. The data stored enable us to audit prescription of drugs, bed occupancy, emergency admissions or any other information we choose to have in the house officer input. The pre-registration residents spend only 2 months in urology. They have welcomed the computerisation and experience few problems. If any information is incorrect it is overwritten when the consultant's entries to the database are typed.

### *Consultant's discharge letter*

The consultant's discharge letter is created by a Foxbase program, which the secretary calls with a single word command. The secretary is asked to input the patient's unit number and the program then uses this to call up the details from the patient database. Figure 2 is a schematic diagram showing how the program produces the letter. Data are taken from the patient database and the resident's discharge letter. The consultant's description of the episode is typed in from a conventionally dictated tape. The program alternates between the word processor for typing free text and database screens for typing or correcting database information. The main entries which are stored in the database are shown in Figure 3, part of the letter. Below the fields are the drugs which were entered by the resident. The program calls these up and enters them automatically. The amount of typing by the secretary is limited to the free text of the letter and any changes made by the consultant to the diagnosis or procedure fields.

### *Urodynamic reporting program*

A program has been developed to generate the



Name: John SMITH
DOB : 12 / 11 / 33
Unit No: 254312
Diagnosis: Prostatism
Admitted: 12.02.89
Treatment: TUR Prostate
Follow-up: Clinic at 6 weeks
Drugs: 1, 11, 113

Drug: Adalat
Form: Tablets
Dose: 10 mg
Frequency: 3
Drug ID : 1

**Fig. 1** Creation of the resident's discharge letter.

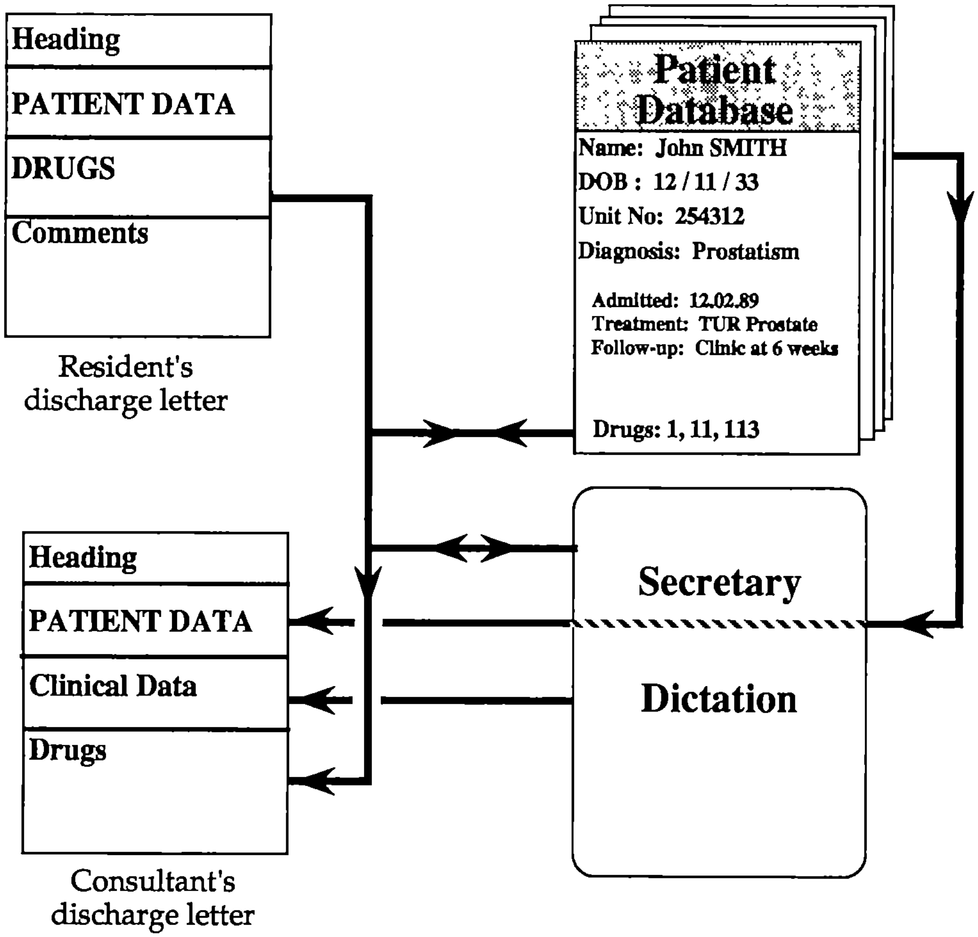


**Fig. 2** Creation of the consultant's discharge letter by the secretary.

```
Admitted :  24.05.89
Discharged: 28.05.89
Consultant: Mr Glen
Diagnosis : Re growth benign prostatic hypertrophy ;
            Previous myocardial  infarct.
Management: TUR prostate at bladder neck, transfused
            2 units of blood
Follow Up : Return clinic in four weeks time


Medication at discharge

Lactulose          10 mls   2 t.i.d.
Ferrous sulphate   200mg    3 t.i.d.
Propantheline      30mg     3 t.i.d.
Co-proxamol        2 tabs   4-6 hourly
Digoxin            0.25mg   mane
Disopyramide       100mg    4 t.i.d.
Piroxicam          10mg     3 t.i.d.
Ampicillin         500mg    3 t.i.d.
```

**Fig. 3** Entries at the bottom of the consultant's letter.

letter the urodynamic specialist sends reporting the results of urodynamics. The schematic is shown in Figure 4. The program accesses 2 principal databases in addition to those already mentioned—one of possible urodynamic findings and one of print statements. The reporting doctor goes through the menu of possible findings, selecting from multiple choice options. After the findings, any treatment can also be recommended by choosing from a menu. The 2 databases are related to one another so that the program simply selects, from the print statements, the entries appropriate to the patient's results. A sample letter is shown in Figure 5. This letter can be generated by the doctor immediately after urodynamic studies and is therefore available much sooner than if it had to be dictated and typed. It also ensures the entry of the urodynamic findings into a database for future use. If the doctor recommends treatment or cystoscopy, the program can send the appropriate message to one of the secretaries. This process is shown in Figure 4. The appointment is entered into the patient's record in the patient database and brought to the secretary's attention the next time that secretary logs onto the system. This is the only work for the secretary in the process.

*Computer history-taking*

The computer history-taking involves the patients answering for themselves with a light pen. At present, owing to the computing power needed to drive the light pen, we have had to use stand-alone personal computers and have not been able to integrate with the multi-user system. Computerised history-taking is an innovation employed to reduce the waiting time for clinic appointments. A large percentage of urological referrals are suitable for a computer history, and the investigative paths for various urological symptoms are easily programmable. The computer system provides a detailed urological and general history. It allows more efficient use of clinical time. The urologist is free to

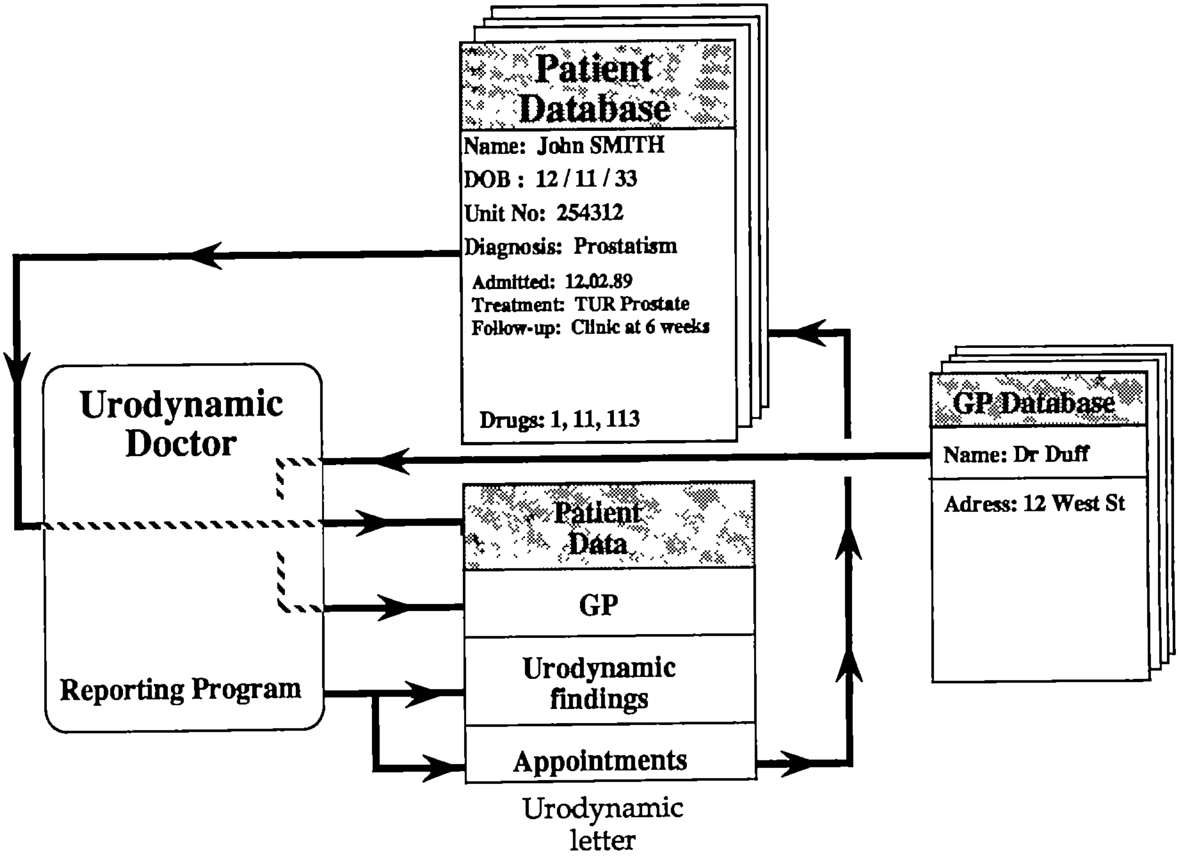


Fig. 4 The use of the urodynamic reporting program.

Urodynamics were performed on 22/01/90. There was a Residual volume of 4ml withdrawn. The bladder held a maximum volume of 336ml.

At Cystometry the bladder was found to be stable hypersensitive of small capacity with both slow and fast filling.

Flow studies demonstrated no difficulty in emptying. The Flow pattern was normal.

The Urethral Pressure Profiles showed the Maximum Urethral Pressure and Closure Pressure to be average with both high and low volume in the bladder.

Provocative Stress tests with the filled bladder produced mild leakage. Leakage was not demonstrated when coughing with a full bladder.

**The urodynamics showed that the bladder is stable hypersensitive and of small capacity. There is no difficulty in emptying. Mild Stress Incontinence was demonstrated.**

The patient will be sent an appointment to return to Mr Glen's Out Patient Clinic to discuss these findings.

I would suggest prescribing terodiline (Micturin) 1-2 tablets twice daily depending on response. This preparation combines anticholinergic action with calcium antagonism.

Yours sincerely,

**Fig. 5** A sample urodynamic report.

concentrate on fine tuning the history with the patients and assessing their attitude to the problem, rather than accumulating the raw data. It has enabled us to reduce the waiting time for a first appointment. Local health centres are encouraged to send patients the same day if their symptoms are urgent. Communication back to the GP is instant, as the patient is encouraged to hand in the computer history and recommendations for management. Our original system was written in Basic on Apple computers (Glen *et al.*, 1989) but we have recently reprogrammed it in DATAFLEX, a database package. The database method has a number of advantages. The questions are each stored as a database record, making it easy to add, remove or change them. The logic of the flow of questions is also stored in the record. For each possible answer to a question, the number of the next question to be asked is stored. There is a special field called a flag field in each record and this is used to trigger any special action. For example, if the question is "Could you be pregnant?" the flag field can be set to ensure that no X-rays or cystoscopy are recommended if the answer is yes. The system has potential as an educational tool. Students can choose a diagnosis and watch how the system takes the history.

The systems running on the multi-user system enable the maintenance of a set of valuable databases. For appropriate users, we have instant recall of the pertinent information for any admission episode for a patient, without need of the case record. An example of the usefulness of this recall would be a GP phone call requesting advice on management. In addition we have access to data which may be required for audit purposes. Because of the multi-user facility there is less repetition of data entry. Users are able to communicate directly. For example, appointments requests can be sent to the secretaries by the urodynamic reporting program.

The department policy of the future will clearly not be a mixture of stand-alone personal computers and a multi-user system, as ours is at present. All applications will run on a single system, so that data are easily transferable. For example, if the urodynamic reporting doctor recommended a cystoscopy, the system would pass that request into an appointment system. Using the Xenix system we have been able to implement a number of related applications. These run smoothly and interface well with the routine work of secretaries, whose work is facilitated and reduced. The clinical efficiency of the department is enhanced.

## Acknowledgement

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# Non-antireflux versus Antireflux Ureteroneocystostomy in Adults

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Summary—A retrospective analysis of ureteric reimplantation in adults showed that a high proportion (71%) had been treated by non-antireflux procedures. Analysis of the ureteroneocystostomy success rate in aetiological groups where either antireflux or non-antireflux techniques were used indicated the superiority of antireflux surgery in the prevention of reflux. The risk of stenosis at the site of anastomosis was equal in both groups. No significant difference in the preservation of renal function was detected in the 2 groups. It was concluded that antireflux procedures offered no advantage over nonantireflux ureteric reimplantation in adults.

Antireflux techniques are usually discussed in reports on ureteric reimplantation into the bladder (Politano and Leadbetter, 1958; Lich *et al.*, 1961; Glenn and Anderson, 1967; Cohen, 1975) and the success rate is approximately 99% (Gonzales *et al.*, 1972; Marberger *et al.*, 1978). In adults, ureteric reimplantation into the bladder is performed for a variety of indications but mainly for urological cancers and trauma. In our experience, non-antireflux ureteroneocystostomy was used in a high proportion of cases. To estimate the success rate of non-antireflux procedures in adults, the results of ureteric non-antireflux and antireflux reimplantation into the bladder were compared in a selected group of patients.

## Patients and Methods

Between 1 January 1970 and 1 January 1986, 20 surgeons reimplanted 458 ureters into the bladder in 412 patients using either the direct method (97%) or the Boari flap (3%). Antireflux ureteroneocystostomy was used almost exclusively in cases of renal transplantation, vesicoureteric reflux and megaureter (Fig.). The Politano-Leadbetter technique was commonly used in routine practice, while the Lich-Gregoir technique was used for allografted ureters. Orr's end-to-side technique was the most commonly used direct non-antireflux technique (Orr, 1950). The results of non-antireflux and antireflux reimplantation of the ureters were compared within the aetiological groups where both operative techniques were used: ureteric anomalies, irradiation injury, non-specific ureteric stenosis, surgical injuries and ureteric tumours (Fig.).

All patients were followed up for 3 to 18 years after surgery. The results were evaluated by comparing renal function with the pre-operative

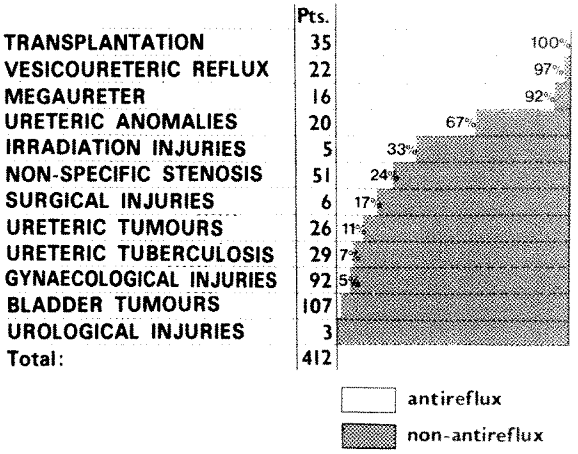

**Fig.** Ratio of non-antireflux to antireflux ureteroneocystostomies in aetiological groups between 1970 and 1986.

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level (creatinine clearance, intravenous urography, scintigraphy and radiorenography) and by evaluating the anastomosis (retrograde cystography: simple, straining, voiding, post-voiding, cystoscopy and retrograde ureteropyelography). The results were analysed by the chi-squared test and Fisher's test of exact probabilities (Siegel, 1956).

## Results

In all, 108 patients (114 ureters) were analysed. The patients' mean age was 46.5 years and the male to female ratio was 55:53; 81 ureters (71%) were subjected to non-antireflux and 33 ureters (29%) to antireflux ureteroneocystostomy. Indications for surgery are given in Table 1. Eighteen patients died (Table 2) and in a further 18 the outcome was not known. The remaining 72 ureters were analysed.

The results of surgery in relation to renal function were assessed in 72 ureterorenal units (63%) (Table 3). Renal function was preserved in 61% of non-antireflux and 74% of antireflux ureteroneocystostomies; this was not statistically significant.

Assessment of the technical results in 72 ureters (67%) indicated a significant difference between the 2 groups (Table 4). This was caused by significantly more reflux (41%) with the non-antireflux technique than with the antireflux technique. Analysis of the results was done by Fisher's exact probability test for each of the aetiological groups but only the ureteric anomalies group contained sufficient patients for a valid assessment. The antireflux technique was more successful in preventing both post-operative reflux and stenosis (($P_{HO}=0.011$). The incidence of obstructed ureters was 22% in both groups, always at the level of the vesicoureteric junction. Stenoses were diagnosed between 15 days and 10 years post-operatively

**Table 1** Indications for Both Types of Ureteroneocystostomy

| Indications | *Ureteroneocystostomy*<br>*Non-antireflux* | <br>*Antireflux* | *No. of ureters (%)* |
|---|---|---|---|
| Irradiation injuries | 4 | 2 | 6 (5) |
| Ureteric anomalies | 7 | 14 | 21 (18) |
| Non-specific stenosis | 41 | 13 | 54 (47) |
| Ureteric tumours | 24 | 3 | 27 (24) |
| Surgical injuries | 5 | 1 | 6 (5) |
| Total | 81 | 33 | 114 (100) |

**Table 2** Cause of Death in 18 Patients after Ureteroneocystostomy

| *Indications* | *No of patients* | *Interval* | *Cause of death* |
|---|---|---|---|
| Irradiation injuries | 1 | 1 year | Cervical tumour |
| | 2 | 8 months | Urosepsis |
| Non-specific stenosis | 3 | 7 years | Unknown |
| | 4 | 6 years | Uraemia |
| | 5 | 9 years | Myocardial infarction |
| | 6 | 7 years | Uraemia |
| Ureteric tumours | 7 | 13 years | Unknown |
| | 8 | 1 year | UUTT* |
| | 9 | 11 years | Myocardial infarction |
| | 10 | 3 years | Unknown |
| | 11 | 2 years | UUTT* |
| | 12 | 1 year | UUTT* |
| | 13 | 4 years | Uraemia |
| | 14 | 2 months | Pulmonary embolus |
| | 15 | 9 months | Uraemia |
| Surgical injuries | 16 | 2 years | Rectal tumour |
| | 17 | 5 years | Colonic tumour |
| | 18 | 3 years | Ovarian tumour |

* Upper urinary tract tumour.

**Table 3** Renal Function after Ureteroneocystostomy

| *Ureteroneocystostomy* | *Renal function*<br>*Same or improved (%)* | <br>*Deteriorated (%)* | *Total no. of renal units (%)* |
|---|---|---|---|
| Non-antireflux | 30 (61) | 19 (39) | 49 (100) |
| Antireflux | 17 (74) | 6 (26) | 23 (100) |
| Total | 47 | 25 | 72 |

$\chi^2=1.112$. df=1. $P>0\ 05$.

**Table 4** Technical Success of Ureteroneocystostomy

| *Uretero-neocystostomy* | *Technical success*<br>*noS/noR** *(%)* | <br>*S†* *(%)* | <br>*R‡* *(%)* | *Total no. of renal units (%)* |
|---|---|---|---|---|
| Non-antireflux | 18 (37) | 11 (22) | 20 (41) | 49 (100) |
| Antireflux | 16 (69) | 5 (22) | 2 (9) | 23 (100) |
| Total | 34 | 16 | 22 | 72 |

$\chi^2=8.86$. df=2. $P<0.05$.

* noS/noR = Absence of stenosis and absence of reflux

† S = Stenosis.

‡ R = Reflux.

(Table 5). Renal function deteriorated in 11 of 16 obstructed ureteroneocystostomies.

## Discussion

Anastomosis is considered technically perfect if it is non-obstructive, does not produce reflux and does not leak. Reflux indicates technical failure in antireflux surgery and surgical errors are often responsible, although the condition of the bladder and infravesical pathways may be contributory factors (De Sy and Oosterlinck, 1978). In cases of non-antireflux ureteroneocystostomy, however, reflux cannot be considered a failure since efforts were not made to avoid it. Thompson *et al.* (1969) suggested that failure of simple ureteroneocystostomy was not due to reflux but to major technical errors leading to stenosis at the site of anastomosis.

A comparative analysis of several series conducted by Debruyne *et al.* (1978) failed to reveal significant differences in the occurrence of post-operative reflux after simple (21/48; 14.2%) and antireflux (28/227; 12.1%) procedures and they advocated simpler surgery even in renal transplantation patients. Lucas *et al.* (1979) agreed with this and reported a 10% incidence of reflux in both types of ureteroneocystostomy with no increased morbidity in transplant patients. In the present series a higher incidence of reflux was recorded in the non-reflux procedures ($\chi^2 = 8.86$, $P < 0.05$). In the groups where both types of ureteroneocystostomy were used there was no significant difference in terms of renal function when compared with the pre-operative levels ($\chi^2 = 1.112$; $P = >0.05$). These findings support the suggestion that reflux in adults does not lead to impaired renal function in patients with normal bladders, non-obstructive infravesical pathways and no urinary infection (Thompson *et al.*, 1969). Stenosis remains the most serious complication. If it occurs unilaterally in a kidney with impaired function it will lead to progressive asymptomatic loss of the kidney. Stenosis may occur as late as 10 years post-operatively. Kinnaert *et al.* (1985) stated that the probability of ureteric stenosis developing at 5 years was 9.7%. Long-term follow-up showed that 22% of patients developed stenosis at the site of anastomosis regardless of the type of ureteroneocystostomy used. The cause of early post-operative failure was oedema and inflammation, urinary leakage, distal ureteric ischaemia, angulation and paravesical scarring. The cause of late stenosis was not known. There were no deaths following surgical correction of stenosis, although 50% of our patients with this complication underwent nephrectomy and 2 are on chronic haemodialysis.

It was concluded that long-term follow-up is necessary to detect stenosis, which should be corrected immediately in order to avoid loss of the kidney. Reflux, however, does not affect ipsilateral

**Table 5** Details of 16 Patients with Stenosis following Ureteroneocystostomy

| *Indications* | *Type of Unc* | *Interval* | *Cause of stenosis* | *Consequences* | *Treatment* | *Outcome* |
|---|---|---|---|---|---|---|
| Irradiation injuries | Non-A | 8.5 years | Irrad. ischaemia | Hydroureteronephrosis | Boari flap | RF stabilisation |
| | Non-A | 2 months | Urine leakage + infection | Hydroureteronephrosis + ac pyelonephritis | Ileal condiut | RF stabilisation |
| Ureteric anomalies | Non-A | 1 year | Unclear | Progressive renal failure | Haemodialysis* | Alive |
| | A | 10 years | Unclear | Renal afunction | Haemodialysis | Alive |
| | A | 11 months | Ureteric stone + scarring | Renal deterioration | Nephrectomy | Alive |
| Non-specific stenosis | Non-A | 5 years | Unclear | Chr. pyelonephritis | Nephrectomy | Alive |
| | Non-A | 7 years | Unclear | Renal afunction | Nephrectomy | Alive |
| | Non-A | 2 months | Oedema + inflammation | Renal exclusion | Nephrostomy def. | Alive |
| | A | 0.5 months | Angulation | Ac. pyelonephritis | Re-Unc Non-A | RF stabilisation |
| | A | 5 years | Unclear | Renal stones | Nephrectomy | Alive |
| Ureteric tumours | Non-A | 4 years | Tumour recurrence | Renal exclusion | Nephroureterectomy | Alive |
| | Non-A | 1 year | Periureteric fibrosis | Hydroureteronephrosis | Re-Unc Non-A | RF stabilisation |
| | Non-A | 3 months | Urine leakage + infection | Intractable pyelonephritis | Nephroureterectomy | Alive |
| | Non-A | 5 months | Progressive scarring | Hydroureteronephrosis | Re-Unc Non-A | RF improvement |
| | A | 5 months | Progressive scarring | Hydroureteronephrosis | Re-Unc Non-A | RF stabilisation |

* Refused repeat ureteroneocystostomy, Unc = Ureteroneocystostomy; RF = Renal function; Non-A = Non-antireflux; A = Antireflux.

kidney function. An antireflux procedure is not necessary for the reimplantation of ureters in adults because renal function is preserved regardless of the surgical technique used.

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# Features of Primary Vesicoureteric Reflux Detected by Prenatal Sonography

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Summary—Primary vesicoureteric reflux (VUR) was detected by prenatal sonography in 34 infants (55 renal units); males accounted for 31 cases. Associated genitourinary anomalies were common, occurring in 29% of the patients. Some element of hydroureteronephrosis was noted at initial cystography in 89% of refluxing renal units, but the degree of renal abnormality at $^{99}$Tc DMSA renography was not predicted by the severity of VUR. Overall, 60% of refluxing renal units were renographically abnormal. Although a high rate of urinary infection was encountered during follow-up, most DMSA assessments were carried out prior to infection and hence likely reflect congenital rather than acquired abnormalities. It was concluded that renal impairment associated with high grade primary VUR is frequently present at birth and not secondary to subsequent infection.

Vesicoureteric reflux is one of many fetal uropathies detectable by prenatal sonography (Scott, 1987); such cases are of interest because renal form and function can be assessed before any secondary effects result from urinary tract infection (UTI) and may provide further clues as to the genesis of reflux nephropathy. At a practical level, there is at least the prospect that early treatment, from the neonatal period onward, might minimise the risk of secondary renal damage.

## Patients and Methods

During the 10-year period to the end of 1989 we saw 309 infants in whom some fetal uropathy had been detected by prenatal sonography and confirmed by postnatal investigation. As described in more detail elsewhere (Rickwood *et al.*, in preparation), our system of investigation did not incorporate routine cystography, even in patients with bilateral anomalies, but rather this investigation was generally restricted to those infants in whom ureteric dilatation was observed by prenatal or postnatal sonography. As a rule, cystography was performed within 1 month of age and, if VUR was confirmed, $^{99}$Tc dimercaptosuccinic acid (DMSA) renography followed at 1 to 3 months of age.

We excluded from the series infants with VUR associated with bladder outflow obstruction, with duplex system ureteroceles and with urethral ureteric ectopia. Somewhat arbitrarily, we also excluded 5 cases where unsuspected contralateral VUR was discovered in the course of investigating other anomalies but, in considering individual renal units, we included such contralateral VUR in infants otherwise qualifying for this series.

VUR was classified according to the recommendations of the International Reflux Study Committee (1981). In infants with one normal kidney on $^{99}$Tc DMSA renography, impairment of the affected kidney was graded "moderate" if differential uptake of isotope lay between 20 and 44% and "severe" if below 20%. In those with bilateral impairment or a solitary kidney, a subjective assessment was made with reference to normal, age-related scans.

Patients routinely received antibiotic prophylaxis, usually trimethoprim 4 mg/kg/day. Urine cultures were obtained on a regular, routine basis and during any pyrexial illness. Cystography and $^{99}$Tc DMSA renography were repeated at 1 to 2

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years of age depending on the clinical course and severity of VUR.

## Results

### *Initial assessment*

A total of 34 patients satisfied the entry criteria for the survey; 31 (91%) were males. Gestational age at which the urinary anomaly was detected ranged from 16 to 39 weeks (mean 29). Mean gestational age at birth was 37.5 weeks and mean birth weight, 3.28 kg, lay at the 50th centile for gestational age.

Associated anomalies are listed in Table 1; ipsilateral pelviureteric junction 'obstruction' was typical of the secondary type often associated with marked VUR, namely with pelvicaliceal dilatation disproportionately greater than that of the ureter, and should not be taken as necessarily implying pelviureteric obstruction in the usual sense of that term.

VUR was present bilaterally in 21 cases (62%), giving a total of 55 renal units for study. The grade of VUR at initial micturating cystography is set out in Table 2; all 6 examples of minor VUR (Grades I and II) were discovered as incidental, contralateral findings. Severe VUR (Grade IV or V) existed in 36 renal units (65%).

The relationship between grade of VUR and findings on $^{99}$Tc DMSA renography is analysed in Figure 1. In patients with moderate impairment, the appearances were sometimes consistent with growth failure (Fig. 2), at others with dysplasia (Fig. 3). No renal impairment was associated with lesser grades of VUR (I/II), but for Grades III to V the degree of renal abnormality could not be predicted by the grade of VUR. In individual cases identical grades of VUR could coexist with normality or moderate impairment (Fig. 3) or with virtual non-function (Fig. 4), and in bilateral VUR impairment could be grossly asymmetrical (Fig. 3). In 8 cases initial $^{99}$Tc DMSA renography was performed after there had been clinical or bacteriological evidence of UTI: among 12 refluxing renal units in this group, 3 were normal but 3 showed appearances consistent with post-infective scarring with moderate impairment. The remaining 43 renal units were assessed by renography prior to any evidence of infection.

**Table 1** Associated Anomalies

| | |
|---|---|
| Genitourinary | |
| Complete duplex, ipsilateral | 5 |
| PUJ obstruction, ipsilateral | 2 |
| Solitary kidney | 2 |
| Undescended testis | 1 |
| Non-genitourinary | |
| Oesophageal atresia | 1 |

**Table 2** Diagnostic Cystogram

| *VUR grade* | *Renal units* |
|---|---|
| I | 1 |
| II | 5 |
| III | 13 |
| IV | 28 |
| V | 8 |

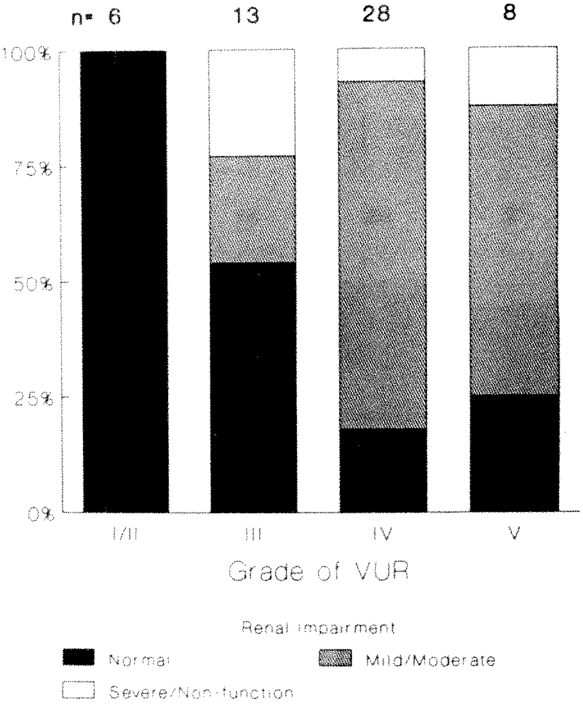

**Fig. 1** DMSA renogram findings: degree of renal impairment as a proportion of the total for each grade of reflux.

### *Progress*

Follow-up ranged from 5 to 78 months (mean 31), during which time 12 patients (35%) had spontaneous urinary infection, 3 of whom were not receiving prophylaxis at the time. In addition, 5 infants (15%) developed urinary infection within a week after (and presumably as a result of) initial cystography.

Fourteen patients (25 refluxing renal units) underwent repeat $^{99}$Tc DMSA renography: in 22 renal units there was no change (including 4 patients who had had symptomatic UTI in the interim). In

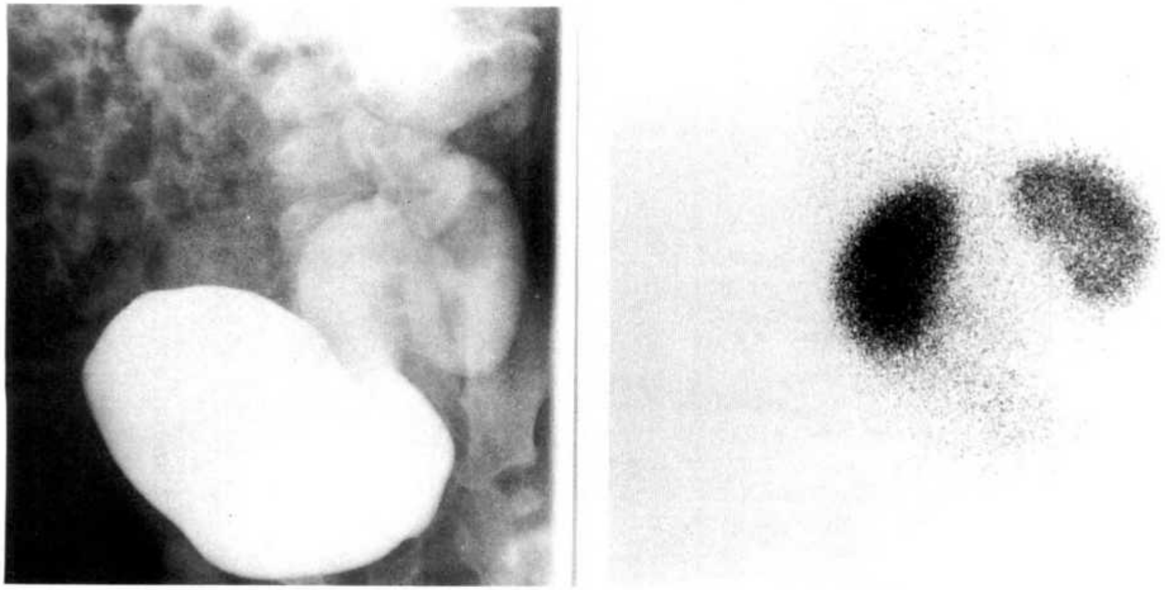

**Fig. 2** (A) Cystogram = unilateral Grade IV VUR. (B) DMSA = small but normally formed kidney.

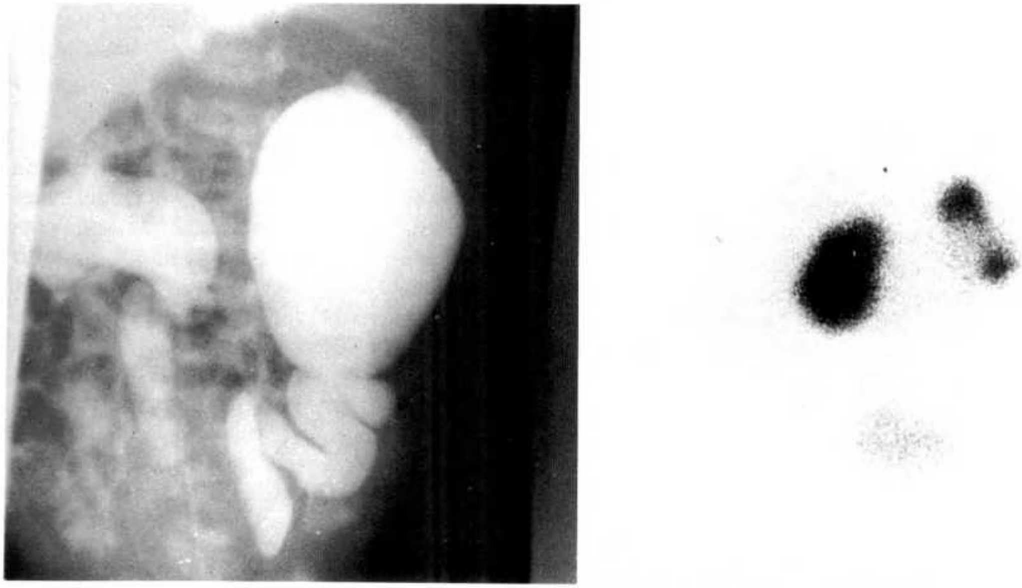

**Fig. 3** (A) Cystogram = bilateral Grade IV VUR. (B) DMSA = left moderately impaired, right normal.

3 renal units, all in patients with unilateral VUR, differential uptake of isotope has decreased; in 1 patient with UTI the change appeared real; in the other 2, without UTI, the appearances could equally well be interpreted as compensatory hypertrophy of the opposite normal kidney.

One patient has had spontaneous resolution of bilateral Grade III VUR documented at 30 months of age; 17 patients remain conservatively managed at a mean 22 months, while 17 (50%) have undergone surgical treatment (14 ureteric reimplantation, 3 nephroureterectomy) at ages ranging from 1 to 72 months (mean 19). Indications were: breakthrough UTI (10) persistent Grade IV or V VUR (4), progressive renal impairment (1), parental preference (2). Nephrectomy specimens showed the histological appearances of severe dysplasia and growth arrest.

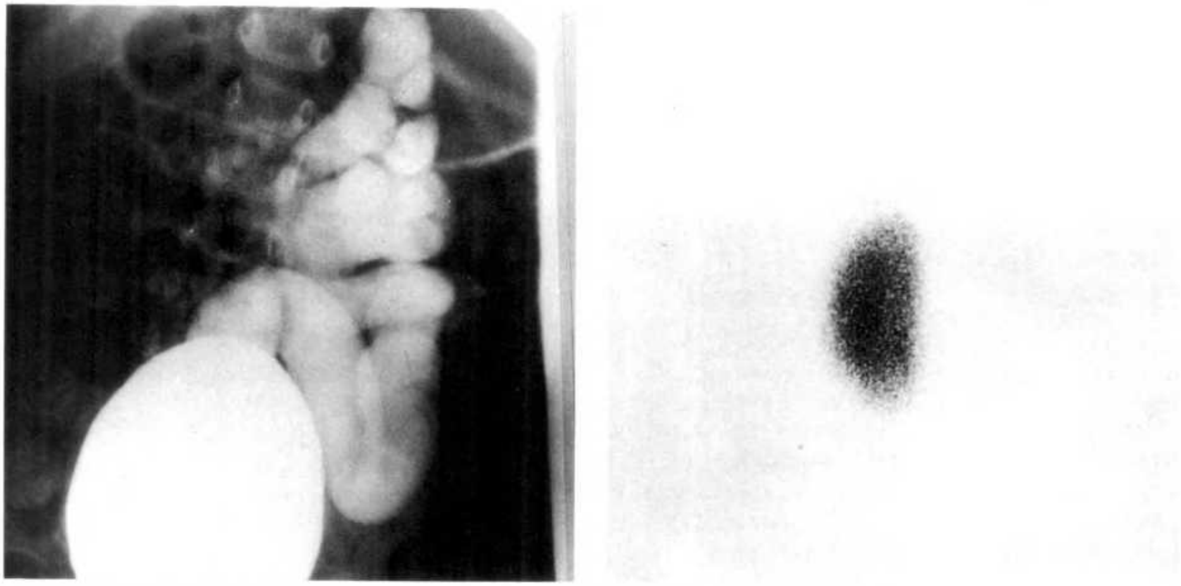

**Fig. 4** (A) Cystogram = unilateral Grade IV VUR. (B) DMSA = non-function on refluxing side.

## Discussion

Our policy for undertaking cystography in infants with prenatally detected uropathies is such as to diagnose only the more severe grades of VUR. Had routine cystography been performed as recommended by Najmaldin *et al.* (1990), more examples of VUR would probably have been detected; whether patients would have benefited thereby is questionable. VUR picked up by such routine cystography tends to be of those lesser degrees rarely associated with renal impairment *ab initio* and likely to resolve spontaneously at an early stage (Gordon *et al.*, 1990). In our series of 307 patients with prenatally diagnosed uropathies (Rickwood *et al.*, in preparation), of whom only those with *known* VUR received antibiotic prophylaxis, the incidence of spontaneous UTI was low (6% excluding cases in the present series); it therefore seems improbable that any number with *unknown* VUR would be at risk of secondary renal damage.

The extreme male preponderance in this series confirms others' findings (Scott, 1987; Paltiel and Lebowitz, 1989; Gordon *et al.*, 1990). Possible reasons are discussed by Gordon *et al.* (1990); one further reason is that the higher voiding pressures in males are apt to cause more ureteric distension and an enhanced chance of detection.

There is every reason to suppose that the urinary tract dilatation seen prenatally in patients in this series was due to fetal VUR; also, because $^{99}$Tc DMSA renography was performed early, in all but 8 cases before there was any clinical or bacteriological evidence of UTI, it seems reasonable to conclude that with these possible exceptions the findings represented the state of the kidneys at birth. In contrast to the findings of Gordon *et al.* (1990), we noted a high incidence of renal impairment at initial $^{99}$Tc DMSA renography, including 6 examples of severe impairment or virtual non-function. This accords with the contention of Mackie and Stephens (1975) that renal impairment associated with VUR may sometimes be congenital rather than acquired, but our findings do not bear out those authors' belief that this relates to supero-lateral or infero-medial ureteric ectopia. In patients coming to ureteric reimplantation in our series, the ureteric orifices were normally sited. In the case illustrated in Figure 3, both orifices were equidistant from the midline and from the bladder neck, yet renal impairment was grossly asymmetrical. Moreover, in 3 prenatally detected examples of unilateral refluxing, single-system urethrally ectopic ureters, renal function, although somewhat reduced (Rickwood *et al.*, in preparation), still exceeded that of several examples in this series with normally sited orifices.

Although renal impairment was not associated with the lesser grades of VUR (which were all incidental findings), we were impressed by the unpredictability of renal damage in individual cases both in terms of severity and nature (hypoplasia versus dysplasia). To date, study of these cases provides few clues, if any, as to the genesis of reflux nephropathy. At the most basic level we do not know whether renal maldevelopment associated with fetal VUR is primary, occurring *pari passu* with VUR, or whether it is secondary, so that maldevelopment is the result of VUR. Perhaps processes are operative with dysplasia resulting from the first and hypoplasia from the second. Whatever the mechanism, it seems highly unlikely that infection plays any part.

At present our experience is too slight both in terms of numbers and period of follow-up to draw more than tentative conclusions as to the natural history and treatment of patients with prenatally detected VUR. The incidence of iatrogenic UTI, from cystography, is appreciable and we now commence antibiotic therapy, in therapeutic dosage, before this examination in infants suspected of having VUR. Once the condition is diagnosed, there is no evident reason for early surgical intervention even where there is gross bilateral VUR. Most of our patients have remained well and have grown normally; the incidence of significant secondary renal damage has been small even in those with UTI. Early experience indicates a tendency for all but the more severe grades of VUR to resolve spontaneously within a comparatively short time (Gordon *et al.*, 1990); our rate of surgical intervention has been greater than in that series, possibly because a larger proportion had renal impairment from the outset.

Despite following conventional practice in administering low-dose antibiotic prophylaxis, the incidence of breakthrough UTI has been considerable. If American experience is valid (Wiswell *et al.*, 1985), male circumcision might reduce the risk of this 10-fold. Alternatively, the concept of antibiotic prophylaxis may itself be flawed, since recent studies indicate that using antibiotics risks exchanging a bowel flora of relatively harmless organisms for one containing more virulent urinary pathogens (Hansson *et al.*, 1989). Controlled prospective trials encompassing both concepts would be welcome.

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# Ambulatory Urodynamics

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Summary—Long-term ambulatory urodynamic monitoring has been employed in 20 patients in an attempt to detect detrusor abnormality not appreciated by conventional cystometry. In 9 female patients with the "urge syndrome" it detected 2 previously unrecognised cases of detrusor instability; in 4 enuretic patients, only 1 of whom was known to be unstable previously, unstable contractions were confirmed, and 2 of 7 cystoplasty patients had high amplitude contractions detected only on ambulatory assessment. The technique provides a more sensitive index of lower urinary tract function than conventional cystometry in such patients.

Ambulatory monitoring of physiological functions has been shown to provide a deeper insight into such functions than static studies in the controlled clinical environment of a laboratory. Much progress has been made in the cardiovascular field using long-term continuous ECG monitoring, and in the gastrointestinal field using oesophageal pH and pressure monitoring.

In urology, the unphysiological nature of conventional urodynamic investigations has always been recognised but within known limitations the technique provides invaluable information on lower urinary tract function and dysfunction. Urethral catheters are invasive and distort the anatomy and physiology of the urethra, but attempts at ambulatory monitoring using either the radiopill (Warrell *et al.*, 1963) or infra-red telemetry have met with difficulties. Thus ambulatory equipment still involves the use of a narrow urethral catheter. A fluid filled system is prone to movement artefact and either an air filled system (James, 1978) or a solid state system (Webb *et al.*, 1989) is required. Storage of data for long-term monitoring is best achieved by either magnetic tape or microprocessor solid state memory.

The long-term monitoring facility enables natural bladder filling to take place and also enables patients to engage in the everyday activities which may precipitate their urinary symptoms.

Because of the widespread use of filling cystometry, the niche for ambulatory studies appears to be the investigation of patients whose symptoms are not accounted for by conventional cystometry and those with postural symptoms or sleep disorders.

## Patients and Methods

Twenty patients, 3 males and 17 females aged between 10 and 60 years, underwent both conventional videourodynamic and ambulatory urodynamic studies. Presenting symptoms included the "urge syndrome" in 9, primary nocturnal and diurnal enuresis in 4 and symptoms of leakage or urgency following reconstructive bladder surgery in 7.

The ambulatory study was performed using Gaeltec catheter mounted pressure transducers, the urethral catheter having a bladder and urethral transducer and a separate rectal catheter having a single transducer. These were linked to a portable battery powered recorder (Type 7MPR) measuring 188 × 67 mm and weighing 650 g, including the 4AA size alkaline batteries. Pressure levels were monitored at 8 samples/s and were stored in a compressed format in semiconductor memory within the unit. Monitoring could be performed for up to 30 h but usually a maximum of 24 h was

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Based on a Poster Demonstration at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

employed. The data were later retrieved by transfer to a desk top computer for analysis on the screen or as hard copy (Fig.). A diary of events and activities was recorded by the patient throughout the monitoring period.

## Results

Day and night ambulatory recordings were obtained on all patients (Table).

The 9 female patients with the "urge syndrome" all had normal conventional urodynamics but in 2 of them involuntary detrusor contractions were detected by ambulatory monitoring. It was also interesting that the amplitude of detrusor contraction during voiding was greater in the majority of patients when assessed by ambulatory cystometry. Of the 4 patients with diurnal and nocturnal enuresis, only 1 had been deemed unstable on conventional assessment, but all showed instability on the ambulatory study.

In the reconstructed group, 6 patients had previously had a clam ileocystoplasty and 1 a caecocystoplasty; 2 clam patients with docile bladders on conventional cystometry showed involuntary contractions up to 100 cm $H_2O$ on ambulatory monitoring. Not surprisingly, low amplitude peristaltic contractions were seen in all but 3 patients.

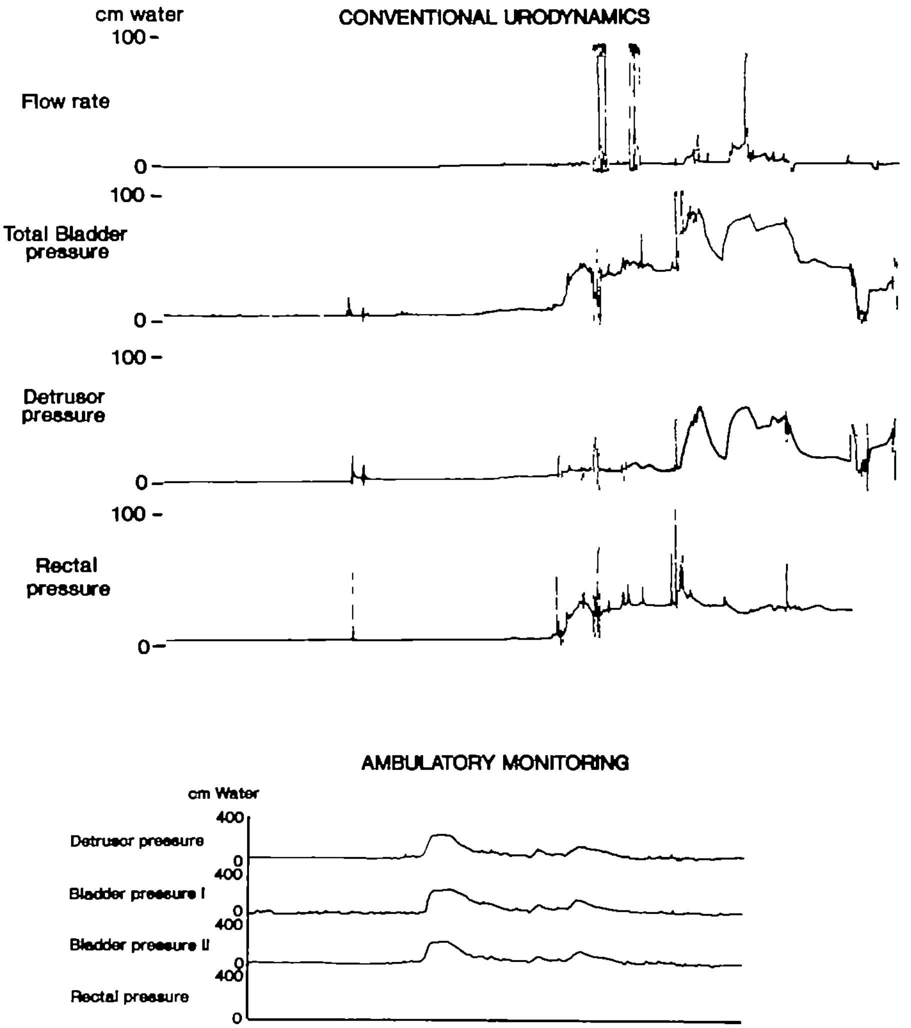

Fig. Conventional and ambulatory urodynamics on the same patient. For the ambulatory study 2 transducers recorded bladder pressure and 1 recorded rectal pressure. No evidence of detrusor instability was detected on filling cystometry, but unstable contractions up to 200 cm $H_2O$ were detected on the ambulatory study.

**Table** Results

A. 9 patients (all female) with the "urge syndrome"

| | Conventional urodynamics | Ambulatory urodynamics |
|---|---|---|
| Normal | 9 | 7 |
| Unstable | 0 | 2 |

B. 4 patients with diurnal and nocturnal enuresis

| | Conventional urodynamics | Ambulatory urodynamics |
|---|---|---|
| Normal | 3 | 0 |
| Unstable | 1 | 4 |

C. 7 patients after reconstructive surgery (6 clam ileocystoplasty) (1 caecocystoplasty)

| | Conventional urodynamics | Ambulatory urodynamics |
|---|---|---|
| Normal (docile) | 4 | 4 |
| Poorly compliant | 3 | 1 |
| Involuntary contractions $>50$ cm $H_2O$ | 0 | 2<br>Low amplitude peristaltic contractions were seen in all but 3 patients |

## Discussion

Ambulatory recording has revolutionised the investigation of other physiological functions and appears well suited to the urodynamic field. The technique we have used is minimally invasive, in keeping with most urodynamic investigations; a possible exception is tocodynamometry, adapted from obstetric practice, which uses only external transducers but is extremely prone to movement artefact. The Gaeltec equipment designed for this study is well tolerated and readily portable.

Ambulatory monitoring in these highly selected groups seems able to detect detrusor abnormality which is not seen on conventional cystometry and may well be ideal for the investigation of patients with postural instability.

The higher voiding pressures noted in this study have been described by others when using ambulatory techniques (Webb *et al.*, 1989, 1990). This may relate to the natural filling rather than the ambulatory nature of the study.

The procedure is time-consuming and we do not propose that it should replace conventional urodynamics; it could, however, be used to supplement them in difficult cases where detrusor abnormality is suspected but not proven. From this study it appears effective in detecting motor defects in reconstructed bladders and those of enuretic patients but less successful in the investigation of the "urge syndrome", where the defect is probably sensory.

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# The Bladder Cooling Test for Urodynamic Assessment: Analysis of 400 Examinations

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Summary—The clinical significance of the bladder cooling test as one part of a standard urodynamic examination was studied in 375 consecutive patients and 25 controls. Inability to perceive cold sensation in the bladder was common in cases of neurogenic lesions and present in nearly half of the patients with outlet obstruction, some with no urodynamic abnormalities and some of the normal subjects. The bladder contractions provoked by the test were clearly associated with detrusor overactivity, as in those patients with upper motor neuron lesions of motor urgency, but 27% of such patients showed no response. In 7 cases the iced water provoked detrusor contractions when cystometry showed no overactivity.

This clinical series confirms that the cold receptors found recently in animal experiments are also present in the human urinary bladder. The bladder cooling test is not an alternative to cystometry, but its inclusion as an integral part of the urodynamic examination seems to be useful, especially in cases where there is also a need to study the sensibility of the bladder at the same time.

Bors' ice-water test was used originally to differentiate between patients with neurogenic bladders of the upper motor neuron type and those with the lower neuron type (Bors, 1957), but has been abandoned in the face of more specific methods. Specific cold receptors with a cooling reflex of high sensitivity have nevertheless been found in the feline bladder mucosa (Fall *et al.*, 1987) and it has been suggested that incorporation of the ice-water test into clinical urodynamic evaluation is of value (Lindström *et al.*, 1988; Fall *et al.*, 1989). To investigate the clinical significance of this proposal, we performed the ice-water test on 375 consecutive patients and 25 controls as part of a standard urodynamic examination.

## Patients and Methods

A total of 375 consecutive patients aged 16 years or more underwent the ice-water test as part of a urodynamic examination that included cystometry, pressure-flow electromyography (EMG), urethral pressure profile measurement and infusion sphincterometry. The methods conformed to the standards proposed by the International Continence Society (Abrams *et al.*, 1988). The cooling test was performed in a supine position by infusing 100 ml of 0°C saline into the empty bladder through a transurethral 8–12F catheter in 20 s and monitoring the intravesical pressure through another catheter (transurethral 4F or suprapubic 8F) for 5 to 8 min. Abdominal pressure was recorded through a rectal balloon catheter. After injection of the iced water the patient was asked if (s)he felt any sensation and, if so, where.

The rise in detrusor pressure recorded after injection of the iced water was assigned to 1 of 3 classes: class I (contraction between 0–2 cm of water), class II (contraction from 3–14 cm of water) and class III (contraction 15 cm of water or more). The patients were also divided into 7 categories on urodynamic and clinical criteria: upper motor neuron lesions, lower motor neuron lesions, outlet obstruction, stress incontinence, motor urgency, non-neurogenic detrusor areflexia or bladder hypotony and normal findings. In addition to this, 25 adults with no urinary symptoms, a normal voided

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volume chart, normal flow rate and absence of residual urine (13 males and 12 females) underwent the ice-water test and the standard urodynamic examination to provide control data.

## Results

Cold sensation upon injection of 100 ml of iced water into the empty bladder was most often missing in cases of upper and lower motor neuron lesions or outlet obstruction, but 3 of the subjects regarded as normal (12%) were also unable to feel the iced water (Table 1).

Class III contractions were most common in patients with upper motor neuron lesions and motor urgency (Table 2), but 27% of the patients in these groups showed no response. No class III contractions were demonstrated in either the normal subjects, the stress incontinence patients or those with no urodynamic abnormalities, and they were also very uncommon in patients with detrusor hypotony and lower motor neuron lesions. Some typical contraction curves are presented in Figures 1 to 4.

**Table 1** Cold Sensation upon Injection of 100 ml Iced Water into the Empty Bladder

| Diagnosis<br>*(no. of patients)* | *Sensation*<br>+ *(%)* | <br>− *(%)* |
|---|---|---|
| Detrusor hypotony, areflexia (58) | 44 (76) | 14 (24) |
| Stress incontinence (33) | 30 (91) | 3 (9) |
| Obstruction (80) | 42 (53) | 38 (47) |
| Lower motor neuron lesion (43) | 23 (53) | 20 (47) |
| Motor urgency (15) | 11 (73) | 4 (27) |
| Upper motor neuron lesion (77) | 46 (60) | 31 (40) |
| No urodynamic abnormalities (69) | 48 (70) | 21 (30) |
| Normal subjects (25) | 22 (88) | 3 (12) |

**Table 2** Detrusor Contraction after Injection of 100 ml Iced Water into the Empty Bladder

| Diagnosis<br>*(no. of patients)* | *Contraction class*<br>*I (%)* | <br>*II (%)* | <br>*III (%)* |
|---|---|---|---|
| Detrusor hypotony, areflexia (58) | 41 (71) | 15 (26) | 2 (3) |
| Stress incontinence (33) | 27 (82) | 6 (18) | 0 |
| Obstruction (80) | 32 (40) | 35 (44) | 13 (16) |
| Lower motor neuron lesion (43) | 27 (63) | 15 (35) | 1 (2) |
| Motor urgency (15) | 4 (27) | 4 (27) | 7 (46) |
| Upper motor neuron lesion (77) | 21 (27) | 18 (23) | 38 (50) |
| No urodynamic abnormalities (69) | 40 (58) | 29 (42) | 0 |
| Normal subjects (25) | 14 (56) | 11 (44) | 0 |

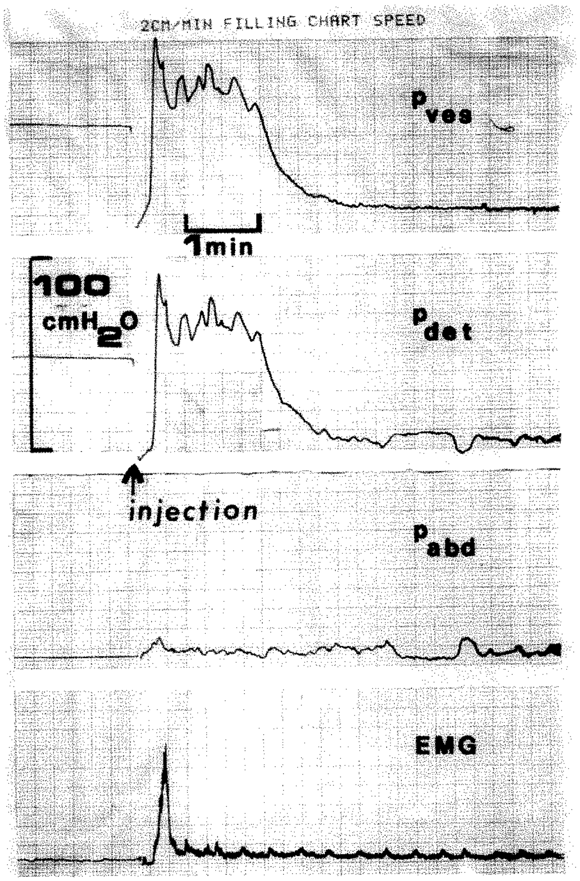

**Fig. 1** Rapid rise in detrusor pressure up to 90 cm of water in 47-year-old female with multiple sclerosis. (Dyssynergic sphincter contraction at the initiation of contraction).

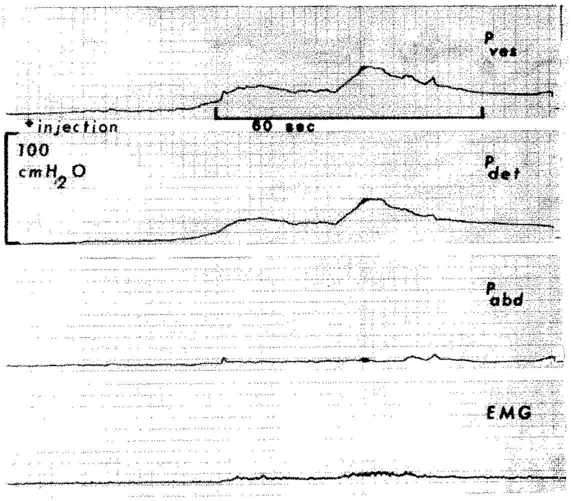

**Fig. 2** Typical contraction curve in 56-year-old female with motor urgency. She had no neurological abnormalities but cystometry revealed instability.

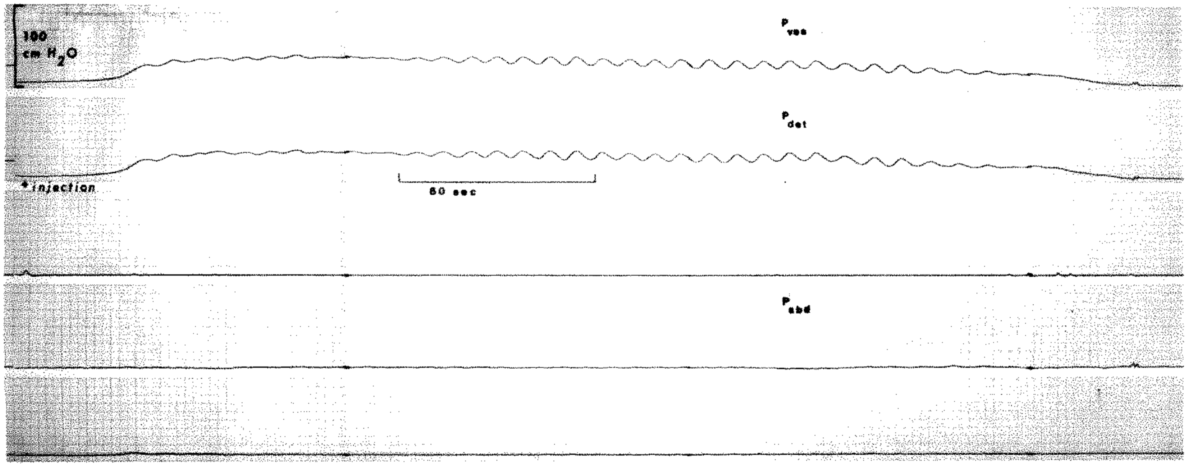

**Fig. 3** Long-standing bladder contraction after injection of iced water in 16-year-old boy who had a fracture in the thoracolumbar border with spinal cord lesion.

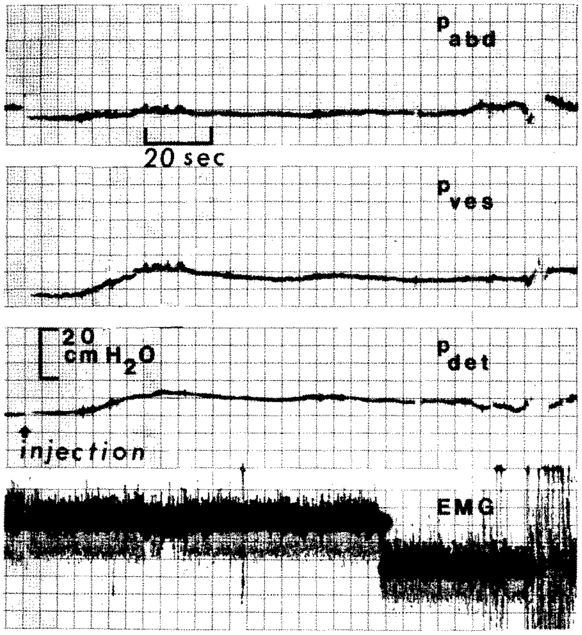

**Fig. 4** Low rise in detrusor pressure (8 cm of water) in 31-year-old female with meningomyelocele and incontinence.

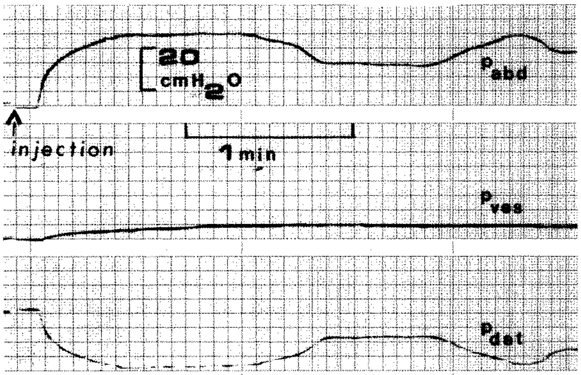

**Fig. 5** Rectal contractions after iced water instillation without rise in bladder pressure in 49-year-old female with stress incontinence.

A total of 97 patients showed detrusor overactivity (instability/hyper-reflexia) on cystometry. The cold water test led to class I contractions in 13 of these patients (13%), class II in 30 (31%) and class III in 54 (56%). On the other hand, a class III response was found in association with stable cystometry in 7 cases. The injection of iced water caused rectal contractions without any rise in bladder pressure in 3 patients (Fig. 5).

There was no clear correlation between a positive bladder cooling reflex and an ability to feel the iced water.

## Discussion

The present series lends much support to the recent theory regarding the existence of a bladder cooling reflex and specific cold receptors (Fall *et al.*, 1987; Lindström *et al.*, 1988). The existence of thermaesthesia of the bladder mucosa has been a source of controversy. Many earlier investigators have denied it (Senger and Rothfeld, 1947; Nathan, 1952; Bors *et al.*, 1956), whereas others have found it obvious (Ray and Neill, 1947; Retief, 1950; McDonald and Murphy, 1959; Gunterberg *et al.*, 1975). It is commonly believed that sensations of stretching and fullness in the bladder are communicated via the parasympathetic nerves and sensations of pain, touch and temperature by sympathetic innervation (Tanagho, 1986). Fall *et al.* (1987) postulated on the basis of feline experiments that a pathway separate from the tension receptor system exists for the bladder cooling reflex, the receptors responsible having properties similar to those of cutaneous cold receptors (Lindström *et al.*, 1988). Our observations support the existence of cold receptors and a cooling reflex in man as well.

Bors *et al.* (1956) pointed out, when examining bladder thermaesthesia, that cold fluid must not contact the urethral mucosa and that small quantities of fluid should be used to avoid the stimulation of adjacent, somatically innervated structures. They claimed that all of their patients with a positive test felt the sensation in the skin and never in the bladder. Contrary to this, however, our patients clearly felt the injected fluid as a cold sensation in the bladder and never in the urethra or skin; an important finding is that our unpublished data show that all patients on whom total cystectomy and bladder substitution had been performed by colocystoplasty lacked cold sensation.

Cold sensation was most often absent in cases of neurogenic lesions. The bladder denervation caused by outflow obstruction (Gosling *et al.*, 1986) may be the reason why nearly half of such patients were not able to feel the cold water, and it may also explain why a class III contraction could be demonstrated in 16% of the patients. Of the 22 patients with total traumatic paraplegia and tetraplegia, 10 (45%) had a cold sensation, showing that the pathways carrying the impulses probably follow sympathetic nerves. Our preliminary impression on the basis of certain cases is that the cold sensation is abolished upon sustaining extensive neurogenic lesions in the pelvis (*e.g.* after extirpation of the rectum). Ray and Neill (1947) also found that interruption of either the sympathetic, parasympathetic or somatic nerve supply did not eliminate bladder sensation. Only interruption of all of these will result in an insensitive bladder. The reason why 3 patients regarded as normal controls had no cold sensation may be that they, nevertheless, had undetermined neuropathy.

Detrusor instability has traditionally been defined as a spontaneous rise in pressure of more than 15 cm of water during cystometry if the patient is asked to inhibit (Bates *et al.*, 1976), although it has been claimed more recently that this threshold is misleading because some unstable detrusor contractions do not develop such a high pressure (Coolsaet and Elhilali, 1988; McGuire, 1988). A detrusor reflex can be elicited by coughing, change of posture, walking and jumping, or by changing the bladder filling medium and filling rate, subcutaneous administration of bethanecol, urethral and anal distension or sleep cystometry (Andersen and Bradley, 1977; Abrams *et al.*, 1988). The technique of "rapid cystometry" by filling the bladder with 100 ml of saline in 3 s can sometimes provoke detrusor contractions (Susset *et al.*, 1981).

The detrusor reflex can be elicited by the ice-water test (Bors, 1957), whereupon a strong contraction ensues either immediately or within a few seconds in patients with a neurogenic bladder of the upper motor neuron type, expelling the catheter. Modern pressure measurement methods enable the contraction to be demonstrated and the force measured (Raz, 1973). Normal subjects and patients with lesions of the lower motor neuron type give a flat curve. It has also been recommended that simultaneous EMG recordings should be performed to demonstrate detrusor-sphincter dyssynergia in cases of upper motor neuron lesions (Sundin and Petersen, 1975).

It has recently been postulated that because of the specific receptor origin and high sensitivity of the cooling test, iced water stimulation could be of value for urodynamic examinations in clinical practice (Lindström *et al.*, 1988; Fall *et al.*, 1989). In the present series, the ice-water test was used systematically as an integral part of the urodynamic examination to study its clinical significance. The results show that if the threshold of 15 cm of water is regarded as significant, the sensitivity of this test for demonstrating detrusor overactivity is poor, since only 56% of the patients with contractions in cystometry showed contractions over this limit after the injection. If contractions of more than 3 cm of water are regarded as significant, the sensitivity increases to 87%. On the other hand, there are some cases of stable cystometry in which the iced water causes a clear detrusor contraction. Thus the method is of some value as a provocation test for eliciting detrusor overactivity, and we regard it as useful at least in cases of suspected detrusor instability when other provocation tests are negative.

None of the stress incontinence patients, the patients with no urodynamic abnormalities or the normal control subjects showed contractions over 15 cm of water after the ice-water injection, while about half of the patients with upper neuron lesions and motor urge did so, the rest remaining below this limit. On the other hand, the test was negative in 27% of the patients in the upper motor neuron group, a much higher figure than the 10% reported previously (Sundin and Petersen, 1975). It is well known, however, that many patients with suprasacral injuries do not show detrusor contraction during cystometry (Light *et al.*, 1985). Consequently some of them also fail to contract after the injection of iced water. One patient with a lower motor neuron lesion and 2 with non-neurogenic detrusor hypotony or areflexia showed class III contractions. Fall *et al.* (1989) recommended the use of Bors' ice-water test as a part of routine cystometry for the classification of overactive bladder function. In cases of "idiopathic detrusor instability" the test should be negative.

The ice-water test cannot replace formal cystometry with its provocation tests, but it does show detrusor overactivity in some cases where cystometry is normal. Different types of detrusor contraction are seen after cold water instillation and the significance of these, like that of contractions of less than 15 cm of water, awaits further evaluation. Our series shows that refinement of the urodynamic diagnosis is really achieved in some cases by using the bladder cooling test. It works not only as a provocation test but also indicates the sensibility of the bladder at the same time. Thus it may be of value, especially in cases of undetermined or suggested neuropathy, in determining whether or not there is any sensory loss in the bladder. The test does not add much more time to the investigation and is well accepted by the patients.

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# Relationship between Bladder Morphology and Long-term Outcome of Treatment in Patients with High Pressure Chronic Retention of Urine

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Summary—A group of 32 men undergoing bladder outflow surgery for high pressure chronic retention (HPCR) of urine were studied prospectively. At the time of treatment marked morphological changes in the bladder wall were demonstrated histologically, but after a mean follow-up of 42.9 months residual urine had decreased significantly and renal function had improved or stabilised in 28 patients (84%). Four patients deteriorated but in 3 of these another potential cause for loss of renal function was present. The majority of patients have a good long-term prognosis following treatment for HPCR.

Patients with bladder outflow obstruction who have chronically distended, thick-walled bladders, bilateral hydroureteronephrosis and long-standing renal impairment have been described as having a "high pressure" form of chronic retention (George *et al.*, 1983). Studies in the early period following corrective bladder outflow surgery showed that, in the absence of infection, recovery of renal function was good (Jones *et al.*, 1988), but to date there are no studies on the long-term efficacy of treatment. A recent report on 19 patients with advanced renal failure due to bladder outflow obstruction identified 5 who had had previous prostatectomies (Sacks *et al.*, 1989), suggesting that surgery is not always successful in preventing upper tract deterioration.

We have assessed the long-term functional recovery following satisfactory bladder outflow surgery for HPCR and compared it with bladder wall morphology measured at the time of treatment in order to determine whether such morphological change can predict poor post-operative recovery.

## Patients and Methods

The study group comprised 32 men aged between 26 and 82 years (mean 62.9) who were diagnosed and treated for HPCR between August 1980 and August 1984. The diagnosis was based on clinical, urodynamic, radiological and biochemical findings; 31 patients had a tense, painless, palpable bladder and the remaining patient had an impalpable bladder with a residual urine of 320 ml. The diagnosis was confirmed in all patients by the finding of abnormally high end-void and end-fill bladder pressures on medium fill cystometry undertaken before drainage of residual urine (George *et al.*, 1983). Bilateral hydroureteronephrosis was identified by either intravenous urography or ultrasound scanning in 31 patients. The remaining patient had an elevated plasma creatinine (0·45 mmol/l) with a palpable bladder, but no upper tract imaging was performed.

Twenty-five patients were subsequently shown to have benign prostatic hypertrophy, 6 had carcinoma of the prostate and 1 a urethral stricture.

Plasma creatinine was estimated in all patients at the time of diagnosis and creatinine clearance was calculated in 28 using a standard 24-h urine collection and plasma sampling clearance technique. Residual urine was measured by catheterisation following completion of the urodynamic studies.

All patients underwent cystoscopy and bladder outflow surgery as appropriate. In 23 patients deep, cold cup, trabecular biopsies were taken from the lateral bladder wall above the ureteric orifice at the

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time of cystoscopy and rapidly frozen in isopentane cooled in liquid nitrogen. At least 2 biopsies were obtained from each patient. Cryostat sections (10 μm thick) were prepared and stained either for routine histology using Masson's trichrome technique or to demonstrate tissue cholinesterase using an adaption of Gomori's method (Gomori, 1952). For all biopsies from each patient the following parameters were measured using a point counting technique (Williams, 1977) previously described in detail (Gilpin *et al.*, 1986; Gosling *et al.*, 1986): (1) area occupied by muscle and area occupied by connective tissue within the muscle bundles of each biopsy; (2) amount of acetylcholinesterase positive nerve present within a representative section of each biopsy. In addition, an assessment of muscle cell mean profile area (MPA) was carried out for each patient from photomicrographs of transversely sectioned smooth muscle bundles (Gosling *et al.*, 1986). For each photomicrograph the total area occupied by smooth muscle was determined by point counting, this area being divided by the actual number of cells present to determine muscle cell MPA for each biopsy.

Clinical follow-up ranged from 6 to 83 months (mean 42.9). Eleven patients died during follow-up, 9 from non-urological disease, 1 from chronic renal failure and 1 from prostatic carcinoma.

Repeated biochemical assessment of renal function was performed in all cases. Plasma creatinine was available in 30 patients and creatinine clearance in 24. Biochemical improvement or deterioration was defined as a change over the baseline value of $>25\%$ (all values in these patients were initially outside the normal range). Biochemical stability was defined as a minor fluctuation in function within the normal range (all values varied $<25\%$). (Normal ranges: plasma creatinine up to 0.12 mmol/l, creatinine clearance >80 ml/min).

Residual urine at follow-up was assessed by post-micturition ultrasound scanning in 26 patients.

Statistical comparisons were made using Student's *t* test and results expressed as ranges with means ±1 SD.

## Results

### *Urodynamic and renal function analysis*

*Residual urine volume.* At presentation ($n = 32$) residual urine ranged from 320 to 2690 ml (mean $= 1360 \pm 586$). At follow-up ($n = 26$) this was significantly reduced, ranging from 0 to 1000 ml (mean $= 193 \pm 259$) ($P < 0.001$) (Fig. 1). At the time of follow-up, residual urine was less than 200 ml in 25 patients; in 5 patients it exceeded 300 ml and in 2 cases it was between 250 and 300 ml. Of these latter 7 patients, 1 had diabetes mellitus with chronic urinary infections, 1 underwent abdominoperineal resection of the rectum and 1 a laminectomy subsequent to their prostatectomy. These factors may have contributed to incomplete bladder emptying.

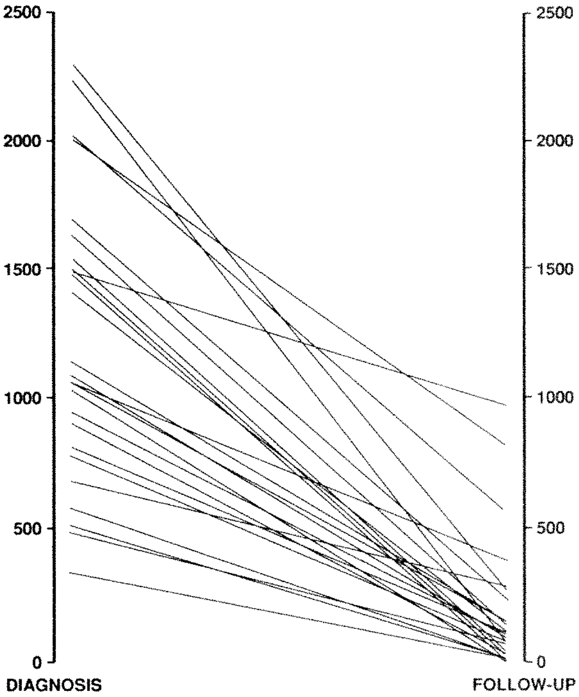

**Fig. 1** Change in residual urine volume (ml) following bladder outflow surgery for HPCR in 26 patients.

*Creatinine clearance.* At presentation ($n = 28$) creatinine clearance ranged from 9 to 122 ml/min (mean $= 53 \pm 35.7$). This improved significantly at follow-up ($n = 24$), ranging from 38 to 164 ml/min (mean $= 81.9 \pm 32.1$) ($P < 0.01$) (Fig. 2).

*Plasma creatinine.* At presentation ($n = 32$) plasma creatinine ranged from 0.07 to 1.63 mmol/l (mean $= 0.24 \pm 0.29$). At follow-up ($n = 30$) it ranged from 0.07 to 0.85 mmol/l (mean $= 0.15 \pm 0.15$); this improvement did not reach statistical significance.

On the basis of creatinine clearance and/or plasma creatinine values, 16 patients showed definite renal functional improvement and 10, who had good function initially, remained stable. In 2 other cases an initial reduction in function was followed by a period of stability exceeding 3 years. Thus 28 of the 32 patients had either improved or stable renal function.

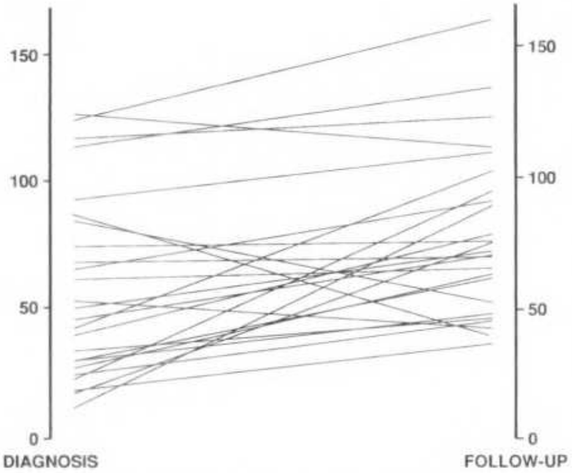

**Fig. 2** Change in creatinine clearance (ml/min) following bladder outflow surgery for HPCR in 24 patients.

There were 4 patients whose renal function deteriorated. One was a diabetic with recurrent urinary infection in whom chronic renal impairment slowly progressed and he died 6 years later. Two had carcinoma of the prostate. One of these improved initially after TURP but both subsequently deteriorated because of malignant lower ureteric obstruction. The fourth patient improved from a creatinine clearance of 52 to 88 ml/min 6 months after prostatectomy but 4 years later this had fallen again to 44 ml/min and he had a residual urine volume of 442 ml.

### *Histology and morphometric analysis*

Biopsy material was available in 23 patients. In all specimens there were varying degrees of connective tissue infiltration within smooth muscle bundles (Fig. 3) together with hypertrophy of detrusor smooth muscle cells. There was also a decrease in the density of acetylcholinesterase-containing nerve fibres. These changes were similar to those previously reported to occur in bladder outflow obstruction (Gilpin *et al.*, 1985; Gosling *et al.*, 1986).

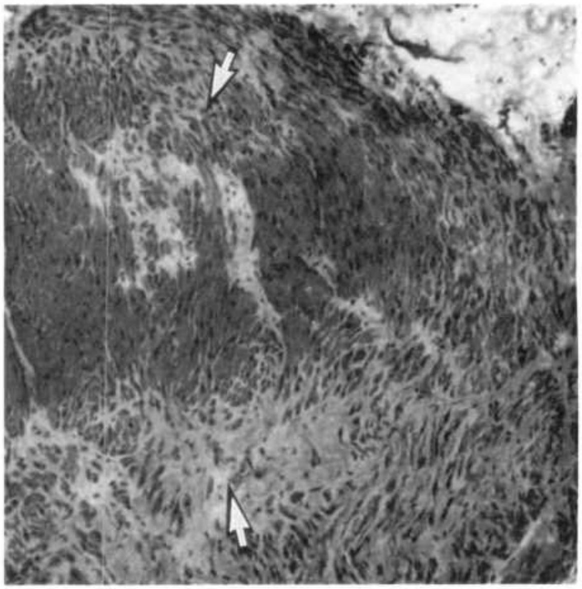

**Fig. 3** Detrusor muscle bundle from patient with HPCR showing marked infiltration by connective tissue (arrows). (Masson's trichrome × 400).

*Muscle/connective tissue ratios.* From the measurements of the amount of muscle compared with the amount of connective tissue present within the muscle bundles, patients were assigned to 1 of 3 categories (Figs 4 and 5). Category 1 contained patients whose detrusor muscle bundles, when sectioned transversely, showed over 60% of the area to be occupied by smooth muscle. From previous studies this appearance is considered to be normal (Gosling *et al.*, 1986). Category 2 contained patients in whom 50 to 60% of the cross-sectional area of their muscle bundles was occupied by smooth muscle cells. Category 3 included patients with less than 50% of their detrusor muscle bundles occupied by muscle. No relationship could be identified between any of these categories and plasma creatinine at diagnosis, biochemical recovery or recovery of bladder emptying.

*Detrusor innervation.* Since the body of the human urinary bladder (the region biopsied in the present study) is innervated almost exclusively by cholinergic nerves, the technique of localising acetylcholinesterase gives a good indication of the density of innervation of each biopsy (Fig. 6). Measurement of the amount of enzyme positive (presumptive cholinergic) nerve for each biopsy produced variable results, with a few patients showing normal innervation density in some areas while in the majority the innervation density was markedly reduced throughout the biopsy. When calculating the innervation density for each patient, a correction factor was applied to adjust for muscle cell hypertrophy in those cases where it occurred. Thus the measured value for the amount of nerve/mm$^2$ for each biopsy was adjusted, using a value for the MPA from a group of "control" patients (Gosling *et al.*, 1986). No correlation between nerve density and plasma creatinine at diagnosis was identified.

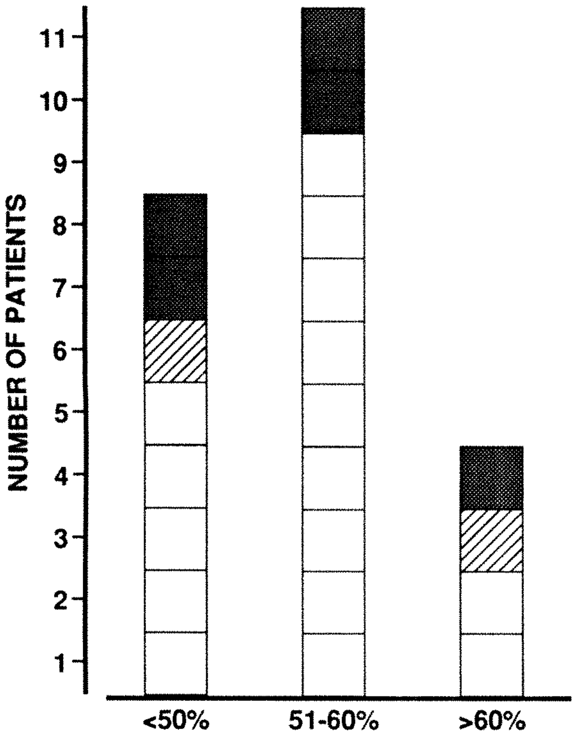

**Fig. 4** Relationship between amount of muscle and collagen seen in detrusor muscle bundles at time of diagnosis and residual urine volume at follow-up in 23 patients after bladder outflow surgery for HPCR. ☐ Residual urine <200 ml. ▨ Residual urine 250–300 ml. ▩ Residual urine >300 ml.

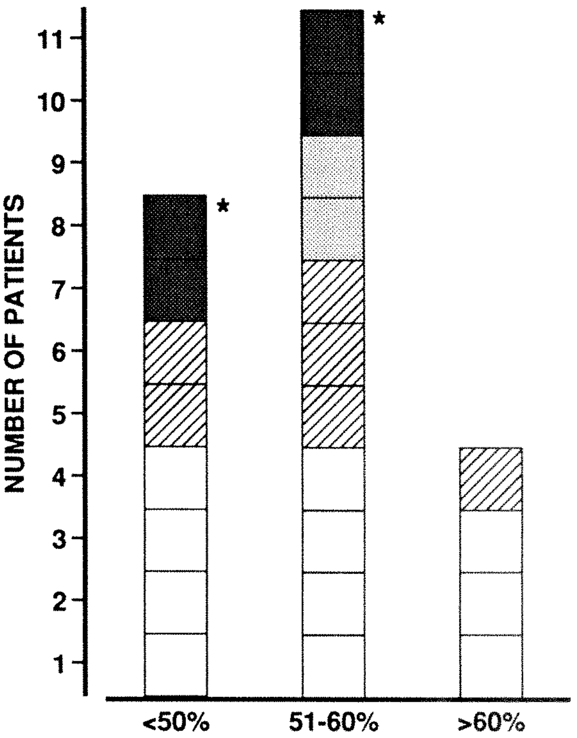

**Fig. 5** Relationship between amount of muscle and collagen seen in detrusor muscle bundles at time of diagnosis and biochemical function at follow-up in 23 patients after bladder outflow surgery for HPCR. ☐ Improved. ▨ Stable. ░ Initial decrease, then stable. ▩ Deterioration. *Initial improvement with deterioration later.

Those patients who emptied their bladders least satisfactorily at follow-up had nerve counts below the mean for the group as a whole. However, there were many patients with similarly poorly innervated detrusors who did empty their bladders well post-operatively. No statistical correlation between nerve counts and residual urine could be identified.

## Discussion

This study has demonstrated that most patients with HPCR had a good result following bladder outflow surgery. Renal function was usually improved or remained stable and bladder emptying was satisfactory in most cases.

At the time of diagnosis, severe structural changes were evident within the bladder of each patient. Connective tissue infiltration was seen in the majority, together with smooth muscle cell hypertrophy and a reduction in the density of

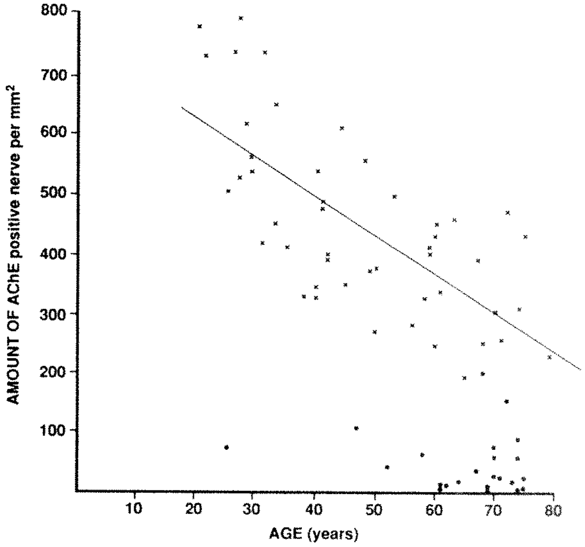

**Fig. 6** Relationship between amount of acetylcholinesterase (AChE) positive nerve and age. Values marked with a cross are control values (Gilpin *et al.*, 1986). Values marked with a dot are from 23 patients undergoing bladder outflow surgery for HPCR.

autonomic innervation. In most cases these changes did not appear to inhibit clinically satisfactory recovery following treatment. There was no apparent relationship between the extent of altered bladder morphology as indicated by the 3 categories of connective infiltration and subsequent clinical outcome. There was a suggestion that poor long-term bladder emptying was related to the reduction in the amount of nervous tissue within the detrusor. Previous studies have shown that the amount of nerve seen in detrusor muscle biopsies decreases with age, and this also occurs in patients with bladder outflow obstruction (Gosling *et al.*, 1986). In the present study the innervation density of the detrusor muscle of each patient was reduced well beyond that predicted for age. The youngest patient (aged 26) showed a marked reduction in the amount of nerve present, suggesting that this had occurred in response to the outflow obstruction.

Whether these histological changes are reversible following relief of obstruction is not known—it was considered unethical to perform repeat cystoscopy and biopsy in patients who were asymptomatic and clinically well. Previous work in animals suggests that the extent of the damage to the detrusor is proportional to the duration of obstruction, with an early reduction in innervation followed later by connective tissue infiltration and muscle cell damage (Dixon *et al.*, 1989). Recovery may also be better following the shorter periods of obstruction seen in the animal model (unpublished observations). Extrapolation of these observations to the clinical situation might imply that earlier diagnosis and treatment of bladder outflow obstruction would be more likely to produce a better post-operative outcome (Gosling *et al.*, 1986) although, as has already been noted, despite severe bladder changes, the outcome was far from unsatisfactory in the majority of patients. It is impossible to say how long these patients had been obstructed or to speculate on the possible relationship between this and the clinical outcome. George (1986a) emphasised that many such patients may have severe yet unsuspected obstruction for a number of years.

Of the 4 patients in this study with diminishing renal function, 3 had another possible explanation for the deterioration (diabetes in 1, carcinoma of the prostate in 2), but it is difficult to distinguish the relative contributions of these pathological processes to renal failure. The fourth patient improved initially but showed signs of deterioration 4 years later. He was asymptomatic and not very fit and declined further evaluation or treatment.

Marked similarities exist between the changes of HPCR in the older man and the condition of non-refluxing posterior urethral valves in children, in whom the bladder wall may become massively hypertrophic (George, 1986b). It has been suggested that 1 cause of poor renal functional recovery following ablation of these valves is persisting upper tract obstruction at the vesicoureteric junction (VUJ) due to chronic, irreversible bladder wall thickening (Hendren *et al.*, 1982). Despite the urodynamic, radiological and renographic similarities between these children and adults with HPCR, it would seem that the results of this study cannot easily be extrapolated to the situation in the child. Severe obstruction to an immature organ undergoing substantial growth during childhood probably means that although the histochemical changes within the bladder wall may be similar to those seen in the adult, the deleterious effect on VUJ transport and subsequently on renal function may be more pronounced.

A recent report on 19 patients with HPCR and severe chronic renal failure presenting to 2 regional nephrology units for dialysis identified 5 who had had previous prostatectomies (Sacks *et al.*, 1989). Initially this would appear to be a relatively high proportion of treatment failures. However, it presumably reflected only a tiny proportion of all men undergoing surgery for HPCR over a number of years within 2 health regions and thus these findings are not incompatible with the relatively good results reported herein.

Two factors may be important in determining a poor ultimate prognosis in this group of patients. Firstly, recurrent bladder outflow obstruction may occur as a result of stricture formation or prostatic regrowth. This emphasises the need to minimise post-TUR stricture formation and to ensure complete resection to the prostatic capsule, especially in younger patients. Secondly, although previous studies from this department on functional recovery in HPCR (Jones *et al.*, 1988) have been in patients without infection, it is well known that the combination of obstruction and sepsis is seriously detrimental to the nephron. Should secondary infection occur, it may therefore explain why some patients ultimately have poor renal function.

It was concluded that the majority of adult patients have a good long-term prognosis following bladder outflow surgery for HPCR, despite developing severe structural changes within the bladder by the time treatment is instituted. Urologists should ensure that patients have satisfactory bladder emptying and are completely free of infection before discharge from follow-up. Younger patients with this condition should probably be placed on some form of long-term surveillance to detect early recurrent obstruction and prevent any future deterioration in renal function.

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# Urodynamic Study of Ileocystoplasty in the Treatment of Idiopathic Detrusor Instability

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Summary—Enterocystoplasty is being used with increasing frequency in the treatment of patients with idiopathic detrusor instability. We have performed a prospective clinical and urodynamic study of this procedure in 11 patients using both conventional (CMG) and ambulatory monitoring techniques (AM).

Nine of 11 patients were satisfied with the symptomatic outcome, but 7 relied on clean intermittent self-catheterisation (CISC) to achieve a good result. Urodynamic studies demonstrated a significant increase in residual urine volume from 48 ± 72 ml before to 347 ± 298 ml after operation, but there was only a small and statistically insignificant increase in cystometric capacity. Detrusor instability, present before operation in all patients, could still be demonstrated in over half of them after operation. However, a significant decrease in the severity of instability was found after operation as assessed by an increased volume at first unstable contraction. The bladder volume before operation at which the first unstable contraction occurred was smaller in those who still had persistent instability after enterocystoplasty compared with those in whom instability could not be identified after operation.

These results suggest that all patients about to undergo ileocystoplasty should be trained in the use of CISC. In selected patients with idiopathic detrusor instability refractory to other treatment, this procedure can yield satisfactory results.

Enterocystoplasty is used in the management of patients with detrusor instability refractory to more conservative forms of treatment. Its use after near-complete bisection of the bladder in the coronal plane was suggested by Bramble (1982) as a suitable treatment for adults with urge incontinence and the effectiveness of this "clam" procedure has been confirmed by subsequent studies (Mundy and Stephenson, 1985; Mundy, 1988; Lewis *et al.*, 1990). However, most series have included patients with or without neuropathic bladder dysfunction and, despite its reported success, little detailed information has been provided concerning the urodynamic findings after operation and the possible mechanisms by which it produces its benefit. We have therefore carried out a prospective clinical and urodynamic study of patients with idiopathic detrusor instability undergoing ileocystoplasty.

## Patients and Methods

Eleven patients (5 men, 6 women; mean age 41 years, range 20–79) were studied. Each patient had disabling symptoms of urgency and urge incontinence and each had been treated intensively before operation without success by means of anticholinergic agents (n = 11), bladder distension (11), endoscopic bladder transection (9) and subtrigonal phenol (7).

### *Operative technique*

Patients underwent ileocystoplasty by the technique described previously (Mundy and Stephenson, 1985). In each case, particular care was taken to divide the bladder down to and in front of the ureteric orifice and in each case a Silastic tube with

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multiple fenestrations was used as a suprapubic catheter. Systemic peri-operative prophylactic antibiotics (ampicillin, gentamicin and metronidazole) were administered for 24 h. The patients were allowed home 8 to 10 days later with both a urethral catheter and a suprapubic catheter *in situ*; they were readmitted a further 10 days later for removal of the catheter.

### *Clinical assessment*

Patients were assessed before and more than 3 months after operation by means of a standard questionnaire (Neal *et al.*, 1987) which scored a range of irritative symptoms up to a maximum of 10. Conventional urodynamic studies (CMG) and ambulatory monitoring (AM) were performed before and between 3 and 18 months after operation.

### *Conventional urodynamic study (CMG)*

A free urinary flow rate and residual urine were measured at the beginning of the study. The conventional urodynamic study was performed at a filling rate of 100 ml/min as described previously (Neal *et al.*, 1987). Residual urine was not emptied before filling, which was continued until the patient felt full or experienced urgency. Provocation tests involved coughing and straining in the supine and erect position and heel bouncing in the erect position.

### *Ambulatory monitoring (AM)*

This was performed as described previously (Griffiths *et al.*, 1989) using a purpose-built module powered by batteries and weighing 750 g. Gaeltec transducers were used to measure bladder and rectal pressures. The data stored in the modules (sample rate of 1 Hz) were transferred to host computer for subsequent play-back, plotting and analysis. During the study the patients were encouraged to lie supine for 1 h but for the remainder of the study (3 h) they were fully mobile. They were allowed to void at will, but residual urine was not emptied. If they complained that a specific activity such as hand washing or washing up resulted in symptoms, an attempt was made to reproduce this activity. The patients were well hydrated and encouraged to drink. They were also fitted with an electronic nappy to detect any urine loss.

### *Statistical analysis*

The terminology used is that of the International Continence Society. The results are reported as means ±1 SD, but results were analysed by tests suitable for non-parametric data, namely the Mann-Whitney test or the Wilcoxon test for paired data.

## Results

There was no post-operative mortality and no patient developed a major wound infection. One man, aged 79 years, developed an incisional hernia 6 months after operation but this has now been repaired. Another patient developed a temporary conduction defect affecting the motor and sensory elements of the right L2 and L3 nerve roots; this was possibly related to a stretch injury of the lumbosacral plexus and slowly resolved over a 6-month period. Early in the study, one young man was readmitted 2 months after operation with severe abdominal pain. A cystogram demonstrated no abnormality, he was treated by urethral catheterisation and antibiotics and his symptoms resolved. In retrospect, his clinical picture was compatible with a spontaneous perforation of the bladder and subsequently he was shown to have developed a significant post-void residual urine; he is now performing regular CISC.

### *Symptomatic outcome*

Before operation, all patients had severe urgency and urge incontinence, their mean symptom score being $7.9 \pm 1$. When reassessed 6 weeks later, the subjective improvement in their symptoms was striking and most were cured of incontinence and severe urgency. However, by the time of the 3-month review, most patients had experienced a recurrence of their symptoms—particularly those of frequency. This appeared to be associated with an increase in residual urine. At this time the irritative symptom score was still $4 \pm 3$.

After urodynamic assessment, including measurement of residual urine, 7 of the 11 patients began clean intermittent self-catheterisation because of voiding dysfunction and recurrent symptoms. Subsequently, there was a marked improvement in symptoms, the mean symptom score being $1 \pm 2$ ($P < 0.01$ compared with before operation). There were 2 clear symptomatic failures. Both patients, despite having a satisfactory urodynamic result (on both CMG and AM), with abolition of detrusor instability and a large functional bladder capacity, complained of severe urinary frequency; one is now managed by means of a permanent urethral catheter.

### *Urodynamic results*

The urodynamic results from both CMG and AM are those obtained whilst the patients voided naturally and before CISC was performed. There was no difference between pre- and post-operative urinary flow rates. The most significant finding was a significant increase in post-void residual urine from 48 ± 72 ml before to 347 ± 298 ml after operation ($P<0.01$) (Fig. 1). The cystometric bladder capacity measured during CMG after operation (353 ± 255 ml) was not significantly greater than that measured before operation (259 ± 135 ml), but total bladder capacity (including residual urine) increased significantly (from 300 ± 150 ml to 680 ml ± 280 ml) ($P<0.01$) (Fig. 2). The increase in mean voided volume measured during AM was not statistically significant (from 140 ± 20 ml to 180 ± 65 ml).

Before operation, detrusor instability was observed in all patients on both CMG and AM. The bladder volume (residual urine plus infused volume) at which the first unstable contraction occurred ranged from 100 to 400 ml (187 ± 105 ml). Post-operatively, unstable contractions persisted in 5 patients during CMG and in 6 during AM, but could not be demonstrated after operation in the remainder ($P<0.01$ compared with before operation). This finding occurred despite the fact that the methods were the same before and after operation and were the same in patients in whom instability was observed and in those in whom it could not be demonstrated. The bladder volume before operation at which the first unstable contraction occurred (residual urine plus infused volume) was significantly smaller in those in whom detrusor instability was persistent (112.5 ± 20 ml) than in those in whom the instability was not apparent (236 ± 110 ml) ($P<0.05$), although total bladder capacity before operation did not differ in these 2 groups (239 ± 68 ml and 363 ± 143 ml). Despite the persistence of the instability after ileocystoplasty, the volume at which the first unstable contraction occurred (residual urine plus infused volume) nevertheless increased in these patients (from 113 ± 19 ml to 398 ± 197 ml) ($P<0.05$) and neither of the patients classed as symptomatic failures had persistent instability after operation. However, the reason for the beneficial increase in bladder capacity was the increase in residual urine—there was little increase in cystometric capacity after operation before CISC was commenced.

Bladder contraction pressures measured during CMG did not change significantly after operation (46 ± 10 cm $H_2O$ *vs* 46 ± 15 cm $H_2O$), whereas there was a significant decrease in these pressure measured by AM (67 ± 20 cm $H_2O$ before and 37 ± 12 cm $H_2O$ after operation) ($P<0.01$). A significant decrease in the mean amplitude of detrusor instability measured during AM was also found after operation (10 ± 13 cm $H_2O$) compared with before (50 ± 24 cm $H_2O$) ($P<0.01$).

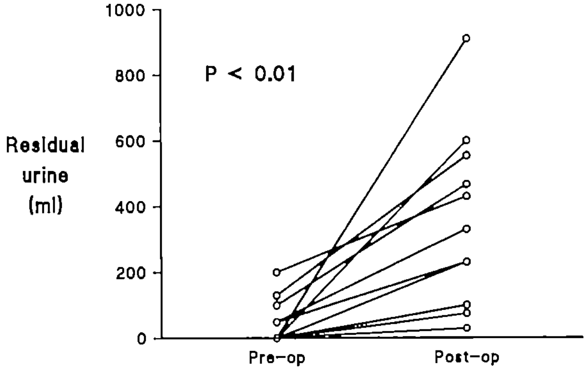

**Fig. 1** Residual urine volumes measured by ultrasound before and more than 3 months after enterocystoplasty.

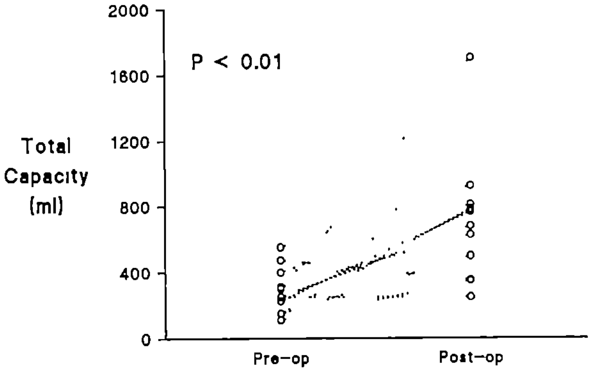

**Fig. 2** Total bladder capacity (residual urine plus cystometric bladder capacity) before and after enterocystoplasty.

## Discussion

Previous studies have shown that ileocystoplasty gives good symptomatic results in patients with urge incontinence (Bramble, 1982; Mundy and Stephenson, 1985), but reports of the effects of this procedure on objective measures of bladder function are scanty. Mundy and Stephenson (1985), studying patients with or without neuropathic bladder dysfunction, reported persistent detrusor instability in 11 of 26 patients and a significant increase in post-voiding residual urine volumes. Only rarely was it severe enough to require CISC in patients without neuropathy (Mundy, 1988). The present study provides a detailed analysis of changes in objective measures of bladder function in a single category of patient: those with idiopathic detrusor instability. It should be noted, however, that these patients were highly selected, all having failed extensive prior medical and surgical treatment before undergoing ileocystoplasty. In the light of this, the eventual symptomatic outcome was very satisfactory, although most had to perform CISC.

The persistence of detrusor instability in approximately half of the patients is in keeping with previous reports (Mundy and Stephenson, 1985); indeed it seems unlikely that division of the detrusor muscle should abolish detrusor instability and there is no reason why insertion of the ileal segment should do so either, although it may make detrusor contraction less efficient. Whilst the methods used in performing the urodynamic study remained constant before and after operation, we cannot be certain whether ileocystoplasty abolishes detrusor instability or whether it merely makes it less evident and more difficult to demonstrate during urodynamic investigation. We favour the latter explanation. It has been pointed out that the increase in functional or cystometric bladder capacity is only modest (Mundy, 1988) and our results are in agreement with this view. However, the increase in total bladder capacity (cystometric capacity plus residual urine) after ileocystoplasty is significant and, although detrusor instability persisted in many patients, it occurred at a greater total bladder capacity and with a decreased amplitude. It is likely that this feature underlies the successful symptomatic outcome of the procedure when patients also perform CISC. It is our impression that the symptomatic outcome immediately after operation is often good. However, after a time residual urine volumes increase, thereby decreasing functional bladder capacity. This decrease in functional capacity, together with the propensity of patients with large residual urines to develop persistent urinary infections, may be the reason why these patients suffer recurrent symptoms of frequency before starting CISC.

Although voiding dysfunction after ileocystoplasty is well recognised, the proportion of patients in our series who had to perform CISC is greater than that reported previously (Mundy and Stephenson, 1985; Mundy, 1988; Lewis *et al.*, 1990). It is possible that our patients were at high risk of voiding dysfunction because they had undergone other procedures such as bladder transection and sub-trigonal injections of phenol. Voiding dysfunction is probably a consequence of inefficient detrusor contraction, for there is no reason to suppose that the operation affects outlet resistance. This inefficient contraction is perhaps the result of division of the detrusor muscle aided by the insertion of a compliant segment of bowel whose contractility is inco-ordinated with the detrusor. One surprising finding, therefore, was that voiding pressures remained unchanged when measured by CMG. We did, however, observe a significant decrease in voiding pressures after ileocystoplasty when patients were studied by AM. The reason for this discrepancy remains uncertain, although we have shown previously that discrepancies occur when voiding pressures are measured during AM and CMG (Webb *et al.*, 1990a).

Another possible reason why low rates of voiding dysfunction have been reported is that the insidious development of large residual urine volumes may not be detected unless the patients are followed up carefully by ultrasound measurement of residual urine on each visit. Previous authors have commented on the high risk of urinary infection that these patients have in the long term; this suggests that their patients also had inefficient bladder emptying. Furthermore, it is now recognised that patients who have undergone various types of enterocystoplasty are at risk of perforation of the neo-bladder (Elder *et al.*, 1988), although this risk should be minimised by ensuring that the patients achieve complete bladder emptying by performing CISC satisfactorily. For these various reasons—quite apart from the possible risk of malignancy in the bowel segment (Stone *et al.*, 1987)—such patients should be followed up carefully.

It therefore appears that the price paid by the patient for improvement in urgency and urge incontinence is not insignificant. In addition to the risk associated with any large surgical procedure, some patients will have problems due to mucus production and a significant proportion need to perform CISC. The latter procedure is acceptable to most patients (Webb *et al.*, 1990b)—even to those with normal urethral sensation—provided they are taught the technique carefully. Thus patients need careful counselling, often on several occasions, before this operation should be performed. We advise teaching the patients to perform CISC beforehand and we would be reluctant to perform ileocystoplasty on patients who cannot manage this procedure.

The clam ileocystoplasty is an effective treatment for patients with severe detrusor instability, but because of these potential drawbacks its use should be reserved for those who have exhausted standard, more conservative treatments.

## Acknowledgements

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# Permanent Urethral Stents for Detrusor Sphincter Dyssynergia

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Summary—A series of 22 patients, most of whom had spinal injuries with detrusor sphincter dyssynergia, have had Medinvent Wallstents placed across the distal mechanism. All but 8 patients had undergone outflow surgery and 11 had had repeated unsuccessful sphincterotomies. The proximal end of the stent was placed over the verumontanum unless fertility was contemplated, when it was placed immediately below the verumontanum.

Fifteen patients achieved complete voiding after placement of the first stent; 3 developed bladder neck obstruction after stenting, but in 1 of these cases resolution occurred after bladder neck incision. The 3 patients with artificial urinary sphincters failed to improve after stenting.

Use of the urethral stent for patients with detrusor sphincter dyssynergia and failed sphincterotomy is a major advance. It should probably be the primary treatment in selected cases. Its effect on fertility is currently under assessment.

Some degree of detrusor sphincter dyssynergia always accompanies suprasacral spinal injury and represents an active contraction of the outflow in association with an involuntary detrusor contraction (Fig. 1) (Bary *et al.*, 1982).

Resting urethral pressure can be reduced by pharmacological means, but the urethral pressures generated during detrusor contraction are rarely affected (Stephenson, 1986) and persistent high volumes of residual urine are common, often with associated infection and autonomic dysreflexia. Endoscopic sphincterotomy has usually been the procedure of choice unless intermittent self-catheterisation is appropriate or an anterior sacral root stimulator suitable. However, even a properly performed sphincterotomy may not achieve adequate bladder emptying, either because the sphincterotomy heals or because high pressures are developed in the urethra by the pelvic floor, and then even multiple sphincterotomies may not prove successful.

The Medinvent Wallstent has been successfully employed in urethral stricture disease (Milroy *et al.*, 1988). We have assessed its role in failed sphincterotomy and as an alternative for detrusor sphincter dyssynergia in patients with neuropathic bladders.

## Patients and Methods

Urethral stents were inserted in 22 patients with detrusor sphincter dyssynergia. Most had suffered spinal injury, but patients with other neurological abnormalities were also included (Table 1). All but 8 patients had undergone previous surgery on the outflow tract, 11 had had repeated sphincterotomies and 3 had artificial urinary sphincters (AUS).

All patients underwent pre-operative urodynamic and radiological assessment; 6 also had a vibratory ejaculation test.

The stent comprises a stainless steel interwoven wire mesh (Fig. 2) which is inserted transurethrally in its compressed state and when released springs open to 40 F diameter (3 cm length). The procedure was usually conducted under general anaesthesia. The stent was placed over the sphincter under

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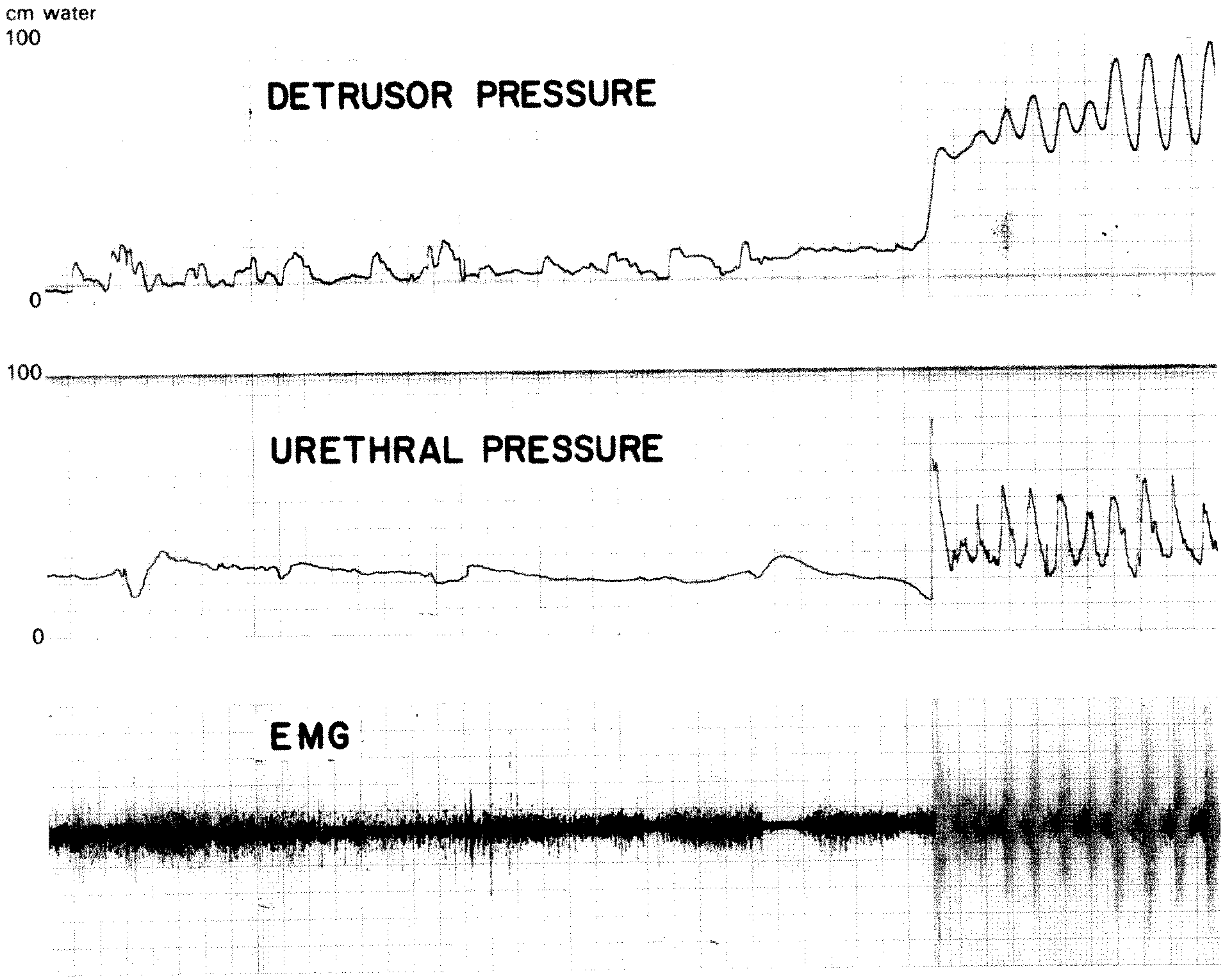

**Fig. 1** Urodynamic tracing demonstrating detrusor sphincter dyssynergia with an increase in urethral sphincter pressure in response to a detrusor contraction.

direct vision. If the patient was potentially fertile the stent was placed just up to the verumontanum. If possible fertility was not a consideration the stent was placed just over the verumontanum.

In the 3 patients with artificial sphincter cuffs the image intensifier was used to place the stent just below the cuff.

Post-operative follow-up included an ascending urethrogram and ultrasound estimation of residual urine volume at 6 weeks. Post-operative vibratory ejaculation tests were also organised.

**Table 1** Dyssynergic Patients

| | |
|---|---|
| Cervical lesions | 12 |
| Thoracic lesions | 1 |
| Spina bifida | 4 |
| Syringomyelia | 2 |
| Multiple sclerosis | 2 |
| Subarachnoid haemorrhage | 1 |
| Total | 22 |

## Results

A maximum follow-up of 1 year has been achieved. Stents were satisfactorily placed in all 22 patients. Two patients with AUS cuffs had elective suprapubic catheterisation during the procedure; 1 patient who underwent simultaneous endoscopic

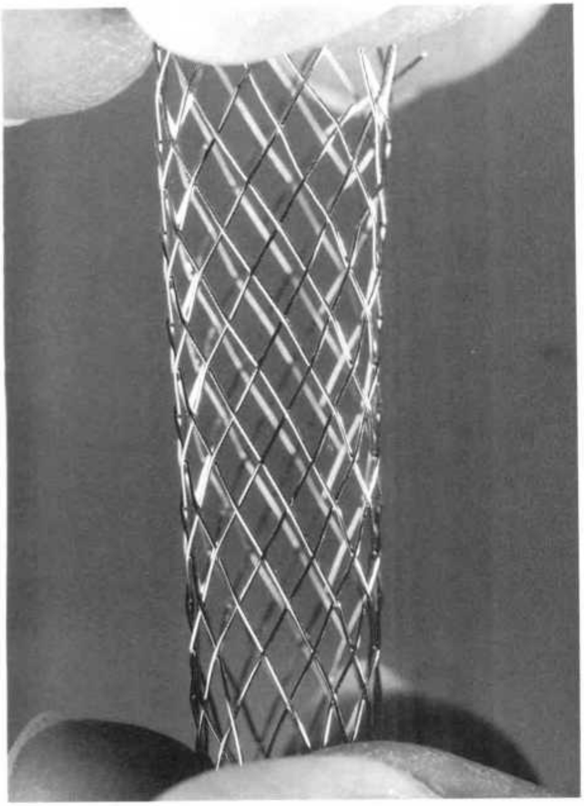

**Fig. 2** The Medinvent Wallstent.

lithopaxy required suprapubic catheterisation for clot retention after stent insertion.

Fifteen patients have had a satisfactory result after insertion of the initial stent (Table 2). Four patients, however, did not void satisfactorily: 1 required a bladder neck incision (BNI), 1 required a bladder neck incision and insertion of 2 further stents, and 2 are awaiting further surgery. One of these had high residual volumes confirmed on ultrasound 6 weeks post-operatively and an ascending urethrogram showed the appearance of mucosal overgrowth through the stent (Fig. 3). Urodynamic tests showed evidence of bladder neck obstruction. None of the patients with an AUS cuff *in situ* improved after stenting; in 1 of these patients, in whom 2 stents had been inserted, the stents had to be removed (with great difficulty) because of perineal discomfort.

In those patients who underwent endoscopy after the procedure, epithelialisation over the stent always occurred and appeared to be complete at 3 months. To date, only 1 patient with a positive preoperative ejaculatory test has had a positive postoperative test; the others have still to be assessed.

**Table 2** Results of Stenting

| | |
|---|---|
| Satisfactory voiding after first stent | 15 |
| Satisfactory voiding after stent and subsequent BNI | 1 |
| Failure to void after 2 stents and BNI | 1 |
| Failure to void—mucosal overgrowth and BN obstruction | 1 |
| Failure to void—second stent awaited | 1 |
| Failure to void after stenting below AUS Cuff | 3 |

## Discussion

Stenting provides a simple and effective technique to counteract detrusor sphincter dyssynergia. In the short term at least it appears superior to sphincterotomy and should be considered in those patients who fail to void satisfactorily after conventional sphincterotomy; it should probably be first-line treatment.

In patients who develop bladder neck obstruction after stenting (Fig. 4) it is probable that the stent holds the sphincter mechanism so wide open that global detrusor hypertrophy results in the subsequent bladder neck obstruction.

In this series the primary stent was usually placed with its proximal margin just below the verumontanum, but in patients in whom overlapping was required there was undoubted residual sphincter activity at the level of the verumontanum. It would therefore be anticipated that covering the verumontanum with the stent would further improve results. This would be acceptable in patients for whom fertility considerations can be disregarded, but the

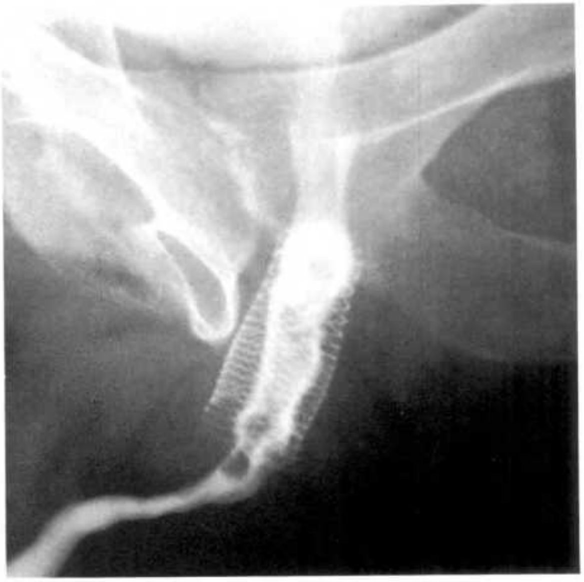

**Fig. 3** Ascending urethrogram showing poor flow of contrast through the stent associated with mucosal overgrowth.

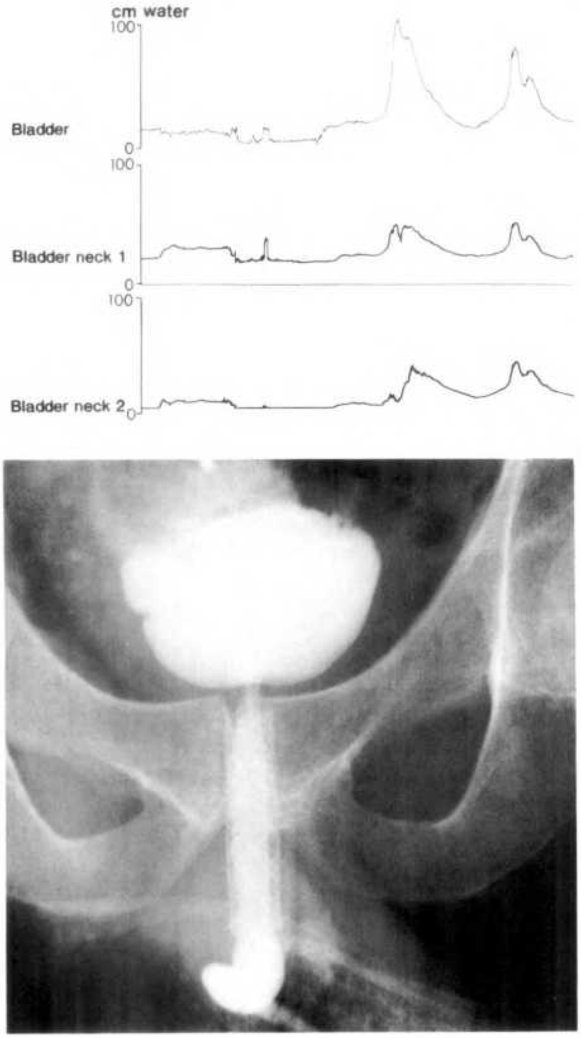

**Fig. 4** Urodynamic study showing bladder neck hypertrophy after stenting. The tracing demonstrates a dyssynergic response of the bladder neck to a hyper-reflexic detrusor contraction. The radiograph shows bladder neck narrowing.

effect of the technique on ejaculation has not been established and a more distal position for the stent remains more appropriate for patients requiring fertility investigation and treatment. It seems almost certain that the stent would obstruct the ejaculatory ducts. On the other hand, it has a beneficial effect on dysreflexia and this is likely to have a detrimental effect on vibratory and electrical ejaculation.

Stenting below an AUS cuff was unsuccessful in this series. Positioning too close to the cuff risks puncture, and if maintaining continence represents a priority in such patients, intermittent self-catheterisation provides a better alternative for those with satisfactory hand function.

The long-term efficacy of urethral stenting remains to be assessed but the encouraging results in this series suggest that the technique represents a major advance in the management of detrusor sphincter dyssynergia after spinal cord injury in selected patients with lower urinary tract neuropathy.

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# Adverse Urinary Symptoms after Total Abdominal Hysterectomy—Fact or Fiction?

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Summary—Urinary symptoms before and after total abdominal hysterectomy in a study group of 80 pre-menopausal women were compared with those in a control group of 78 pre-menopausal women who had dilatation and curettage alone. No urinary symptom was found more commonly after hysterectomy than after curettage, whilst stress incontinence was less common in the study group. Transient symptoms occurred more frequently after hysterectomy.

Hysterectomy has been implicated as the cause of a variety of urinary symptoms including the urethral syndrome (Hanley, 1969; Smith *et al.*, 1970), stress incontinence, detrusor instability and voiding difficulties (Farghaly *et al.*, 1986). There is limited evidence to support these claims and the question remains—is total abdominal hysterectomy responsible for causing adverse lower urinary tract symptoms?

A prospective, controlled trial was devised to compare urinary symptoms after total abdominal hysterectomy with those following dilatation and curettage—a procedure which has no influence on lower urinary tract function but is performed on similar patients for similar gynaecological complaints.

## Patients and Methods

During an 18-month period all pre-menopausal patients under the care of one consultant unit and undergoing total abdominal hysterectomy for benign disease, or dilatation and curettage (D & C) in the absence of malignancy, had urinary symptoms elicited pre-operatively on a standard questionnaire. The presence of frequency (voiding $>7$ times per day), nocturia (twice or more per night), stress incontinence, urgency, urge incontinence, voiding difficulties or recurrent urinary tract infections were sought. Age, parity, daily fluid intake, smoking habit and drug history were also documented. The presence of a pelvic mass (ovarian cyst $>10$ cm diameter or a uterus $>10$ weeks' size) excluded any patient from the study.

A post-operative questionnaire was sent to each patient asking her to document any current or transient urinary symptoms (follow-up 3–21 months).

Symptoms before and after total abdominal hysterectomy were compared statistically with those before and after D & C using the chi-squared test. The unpaired Student's *t* test demonstrated that the 2 groups were well matched for age, smoking habit, parity and fluid intake.

## Results

Patients undergoing hysterectomy did so for menstrual disturbance unresponsive to conservative measures, recurrent atypical smears or pelvic pain. Dilatation and curettage was performed for menstrual disorder. The 2 groups, being similar in their presentation, were found to be matched for age, parity, smoking habit and daily fluid intake (Table 1).

A total of 131 post-operative questionnaires were sent to patients in the control group (D & C) and 78 replies were received (59.5%); 119 forms were sent to patients in the study group (hysterectomy) and 80 replied (67.2%).

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**Table 1** Comparison of Study Group versus Control Group

| | *D & C (n=78)* | *Hysterectomy (n=80)* | *Significance* |
|---|---|---|---|
| Age (years) | Mean 41.72<br>Range 23–57<br>SD 7.54 | Mean 42.33<br>Range 23–55<br>SD 7.48 | N/S |
| Fluid intake (cups/day) | Mean 7.27<br>SD 2.28 | Mean 7.72<br>SD 2.90 | N/S |
| Smoking habit (cigs/day) | Mean 16.23<br>SD 5.38 | Mean 17.32<br>SD 9.08 | N/S |
| Parity | Nullipara 14<br>Para 1 13<br>Para 2+ 51 | Nullipara 8<br>Para 1 16<br>Para 2+ 56 | N/S |

**Table 3** Transient Urinary Complaints after Hysterectomy

| *Symptom* | *No. of Patients* |
|---|---|
| Urgency | 8 |
| Frequency | 7 |
| Pain on micturition | 6 |
| Hesitancy | 2 |
| Urinary tract infections | 2 |
| Urinary leakage | 1 |
| Nocturia | 1 |

No urinary symptom occurred more frequently after hysterectomy than after D & C and this was also true for the triad of frequency, urgency and urge incontinence suggestive of detrusor instability (Table 2). Stress incontinence was found to be less frequent after hysterectomy ($P<0.05$).

As may be expected, transient urinary disturbance is more commonly and more definitely described after hysterectomy ($P<0.05$) (Table 3). Urgency, frequency and pain on micturition were the most common complaints and these symptoms took between 3 days and 3 months to resolve. Twelve patients (15%) claimed that hysterectomy was directly responsible for curing adverse urinary symptoms.

## Discussion

In 1969, Hanley voiced a widely held view that total abdominal hysterectomy may be directly responsible for the development of debilitating urinary symptoms. Scientific evidence in support of these claims is limited. Smith *et al.* (1970) and Farghaly *et al.* (1986) reported uncontrolled studies linking hysterectomy to the onset of stress incontinence, the urethral syndrome, detrusor instability and voiding difficulties, whilst Parys *et al.* (1989) were able to demonstrate longer sacral reflex latency after hysterectomy which may be linked to the vesicourethral dysfunction. However, Mundy (1982), in his cadaver dissections, was unable to explain anatomically why significant damage to the pelvic nerves should occur. The pelvic parasympathetics and the pelvic plexus lie mostly below the cardinal ligaments, making damage at hysterectomy unlikely unless radical hysterectomy and excision of a vaginal cuff are performed.

Jequier (1976) pointed out a high incidence of changeable urinary symptoms in peri-menopausal women, most women undergoing hysterectomy falling into this age group. This case controlled study confirmed that urinary symptoms occurred no more frequently after hysterectomy than would have occurred by chance alone. Protection against the development of stress incontinence was an unexpected observation. In addition, 3 patients were cured of pre-existing stress incontinence by hysterectomy. Parys *et al.* (1989) attributed such an improvement to urethral obstruction in their patients but fixation of the vaginal vault to the utero-

**Table 2** Urinary Symptoms before and after Hysterectomy and D & C

| | *D & C (n=78)* | | *Hysterectomy (n=80)* | | |
|---|---|---|---|---|---|
| *Symptom* | *Before* | *After* | *Before* | *After* | *Chi-squared test* |
| Frequency | 5 | 20 | 5 | 28 | N/S |
| Nocturia | 5 | 18 | 1 | 13 | N/S |
| Urgency | 3 | 21 | 6 | 27 | N/S |
| Urge incontinence | 2 | 15 | 5 | 25 | N/S |
| Stress incontinence | 1 | 25 | 4 | 16 | $P<0.05$ |
| Recurrent urinary tract infection | 0 | 1 | 1 | 4 | N/S |
| Voiding problems | 2 | 7 | 0 | 5 | N/S |
| Frequency, urgency+urge incontinence | 1 | 9 | 3 | 8 | N/S |
| Transient symptoms | | 8 | | 22 | $P<0.05$ |

sacral ligaments may achieve bladder neck elevation and provide an alternative explanation.

As may be expected, and confirming the observational study of Wake (1980), transient symptoms proved more common in the study group. Only 1 patient complained of troublesome and persisting urinary problems whose onset was directly related to hysterectomy. This patient, who has mixed symptoms of stress and urge incontinence, is currently undergoing urodynamic assessment.

Only 5 patients complained of post-operative voiding difficulties, which is in contrast to the high incidence in the series reported by Parys *et al.* (1989), whose conclusion supported the view of Mundy (1982) that careful surgical technique by taking the uterine artery pedicles close to the uterus and minimal dissection of the bladder from the cervix and vagina may minimise pelvic nerve damage.

It was disappointing that the response rate to our postoperative questionnaire was only 63.2% overall despite a second form being sent to patients who failed to respond to the first. We feel, however, that patients would be more likely to repond to our survey if they had significant urinary complaints. To support this assumption, the case records were reviewed of each patient who did not reply to ascertain whether they had been referred to another gynaecological or urological team with urinary complaints. No such referral was found.

Lower urinary tract symptoms are common and changeable in peri-menopausal women. This study is unable to confirm the view that hysterectomy increases the incidence of urinary symptoms compared with a control group and indicates a possible protective effect against the development of stress incontinence. Since the numbers in this preliminary study are small, we intend to continue our observations to confirm or deny our findings in a larger series.

It is assumed that D & C has no effect on lower urinary tract symptoms, but a significant number of patients described symptoms appearing after the procedure. It is likely that this represents the "background incidence" of developing urinary symptoms in patients in this study but it may be that patients find it easier to reveal urinary symptoms on a postal questionnaire than directly to a doctor in a gynaecological clinic, whilst other patients may respond to the suggestion of repeated questioning. Since both control and study groups were subject to the same conditions, however, this theoretical effect is statistically irrelevant.

There is no evidence to support the view that sub-total hysterectomy should be routinely performed to protect against bladder and urethral dysfunction, particularly in the light of increasing detection of cervical intra-epithelial neoplasia and cervical cancer.

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# Functional and Urodynamic Characteristics of Bladder Substitution with Detubularised Right Colonic Segment

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Summary—A total of 19 patients underwent bladder replacement with a detubularised right colonic segment; 14 males underwent complete substitution after cystoprostatectomy and 5 females had augmentation after subtotal cystectomy. The mean follow-up time was 20 months. Urodynamic evaluation showed a low pressure reservoir with a mean capacity of 580 ml and normal closure pressure. Sensitivity of the bladder to cold was normal in the augmentation group but was lacking in all patients in the total substitution group. In all except 1 patient the neobladder emptied effectively upon straining without significant residual urine. Seventeen patients were completely continent by day and 10 by night; 1 patient developed hyperchloraemic acidosis requiring treatment.

Bladder substitution is superior to the standard ileal or colonic conduits with regard to quality of life, and the use of a right colonic segment is functionally comparable with neobladders composed of the ileum or a combination of the right colon and ileum. The latter are more difficult to fabricate and so may have more complications.

Replacement of the bladder with a bowel reservoir which allows continence and maintains the normal voiding route has gained wide acceptance during the last 10 years because of the unsatisfactory long-term results of ileal and colonic conduits and the increasing number of patients who prefer a more socially acceptable form of urinary diversion (Daughtry *et al.*, 1977; Ackermann and Ebert, 1985). In an attempt to avoid the problems associated with conduits, several forms of bladder substitution have been introduced in order to create an intra-abdominal urinary reservoir, combining the physiological advantages of urinary continence with physiological conditions of renal protection (Camey and LeDuc, 1979; Kock *et al.*, 1982; Månsson *et al.*, 1984; Thueroff *et al.*, 1985, 1986; Light and Engelmann, 1986). Various bowel segments and configurations have been evaluated for bladder replacement, but no consensus has been reached on which is the best. Nevertheless, a greater understanding of the physical and physiological characteristics of intestinal segments for bladder substitution has led to a realisation of the importance of detubularisation in order to avoid high pressure contractions (Goldwasser *et al.*, 1987; Hinman, 1988).

Since January 1987 we have been using a detubularised right colonic segment as a bladder replacement (Goldwasser *et al.*, 1986). We now report on the functional characteristics of this neobladder.

## Patients and Methods

Nineteen patients underwent bladder substitution with a detubularised right colon segment between January 1987 and October 1989. Fourteen men (aged 47–77 years, mean 64) underwent total

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bladder replacement after radical cystoprostatectomy for invasive bladder cancer, and 3 women with interstitial cystitis, 1 with severe bladder dysfunction and 1 with a contracted bladder and vesico-vaginal fistula due to previous radiotherapy, were subjected to subtotal cystectomy and augmentation. The ages of the female patients ranged from 27 to 66 years (mean 54). The follow-up time for these 19 patients was 7 to 36 months (mean 20). The technique of bladder replacement was as described by Goldwasser *et al.* (1986). The caecum, ascending colon and proximal part of the transverse colon were isolated on a mesenteric pedicle that included the ileocolic artery and the right colonic artery. If necessary, however, the right colonic artery was divided in order to permit detubularisation and a tension-free anastomosis of the bladder substitute to the urethra. The ureters were implanted into the bowel segment using the Goodwin technique of submucosal tunnelling. The pouch was drained with a transurethral 20 F Foley catheter for 3 weeks. Ureteric stents, and also a 14 F Malecot catheter in the first 7 patients, were led out through the anterior wall of the substitute bladder and removed after 2 weeks.

Post-operative examination at 3-monthly intervals included tests of the urine, renal function, electrolyte and acid base balance, ultrasound of the kidneys and, if necessary, intravenous urography (IVU), evaluation of the patient's history with regard to urinary continence, voiding conditions (micturition list) and satisfaction. In addition, IVU, voiding cystography and urodynamic evaluation of the neobladders were performed 6 months after the operation. The urodynamic investigation included measurement of post-void residual volume, water cystometry with a filling rate of 50 ml/min, pressure flow EMG measurements with a 4 F catheter in the urethra and urethral pressure profile measurements. The methods, definitions and units conformed to the standards proposed by the International Continence Society (Abrams *et al.*, 1988). The capacity of the reservoir, its pressure at 50% and 100% capacity, volume at the first uninhibited contraction (if present), amplitude of maximum uninhibited contraction, maximum reservoir pressure generated, compliance, reservoir pressure during micturition, peak flow rate and maximum urethral closure pressure were recorded. In addition, the sensitivity and reactivity of the neobladder were investigated with the bladder cooling test, using 100 ml of saline at 0°C in 10 patients, 7 total substitutions and 3 augmentations (Bors, 1957; Tammela *et al.*, 1989). Two patients were not examined urodynamically or radiologically at 6 months, 1 because of progression of bladder cancer and the other because of pregnancy (the youngest augmentation patient).

## Results

There was no operative mortality. Convalescence was complicated in 3 patients (1 with a prolonged ileus and 2 with minor wound infections). Late complications are listed in Table 1. One patient developed hyperchloraemic acidosis which required treatment with alkalising drugs. Three patients had problems with mucus secretion during the first few months but only 1 of these had occasional urinary retention. These situations were treated by self-catheterisation. Voiding cystography did not reveal reflux in any patient.

Day-time continence was achieved in 12 of the 14 patients in the complete bladder substitution group 6 months post-operatively (86%), but night-time continence was achieved in only 6 patients (43%), including the one who emptied the reservoir by intermittent catheterisation. This was resorted to because of incomplete emptying of the neobladder. All 5 patients in the augmentation group were continent by day and only 1 suffered from occasional night-time incontinence. The micturition intervals ranged from 2 to 4 h (mean 3.4) and voided volumes from 150 to 650 ml. Most of the patients experienced filling of the neobladder as a fullness in the lower abdomen and groins. One patient lacked any recognisable sensation of reservoir fullness, however, and therefore voided at regular intervals to avoid overdistension.

The capacity of the neobladder at cystometry varied between 320 and 900 ml (mean 580) with a mean compliance of 40 ml/cm$H_2O$ (Table 2). Mean reservoir pressure was 20 cm of water (range 6–72) with a half-full neobladder and 34 cm of water (10–100) with a full neobladder. In 7 patients cystometry

**Table 1** Late Complications and their Treatment after Bladder Substitution with a Detubularised Right Colonic Segment

| *Complication* | *No. of patients* | *Treatment* |
|---|---|---|
| Ureterointestinal stricture | 2 | Operative repair |
| Ileus | 1 | Conservative |
| Post-operative hernia | 2 | Operative repair |
| Hyperchloraemic acidosis | 1 | Alkalising drugs |
| Incomplete emptying of the neobladder | 1 | Intermittent catheterisation |

**Table 2** Summary of Urodynamic Characteristics of the Detubularised Right Colonic Neobladder

| | *Mean* | *Range* |
|---|---|---|
| Capacity (ml) | 580 | (320–900) |
| Compliance (ml/cm$H_2O$) | 40 | (7.2–162) |
| Reservoir pressure (cm of water) | | |
| at 100% capacity | 20 | (6–72) |
| at 50% capacity | 34 | (10–100) |
| Volume at first uninhibited contraction (ml), if present (10/15 pts) | 295 | (150–450) |
| Amplitude of maximum uninhibited contraction, if present (10/15 pts) | 26 5 | (15–45) |
| Maximum reservoir pressure generated (cm of water) | 43 | (10–110) |
| Reservoir pressure during micturition (cm of water) | 89 | (28–210) |
| Post-void residual urine (ml) | 36 | (0–110) |

revealed no significant contractions ($> 15$ cm$H_2O$), while in 10 patients the mean volume of the first significant contraction was 290 ml (range 150–450). The amplitude of the maximum uninhibited contraction ranged from 15 to 45 cm of water (mean 26.5) and the maximum reservoir pressure generated from 10 to 110 cm of water (mean 43). All patients voided by abdominal straining, with a mean maximum reservoir pressure of 89 cm of water (range 28–210) and a peak flow rate of 24 ml/s (range 13–45). Post-void residual urine was between 0 and 110 ml (mean 36).

The mean maximum urethral closure pressure in the males with complete bladder substitution was 70 cm of water with a single pressure peak, whilst that in the females with the augmentation was 44 cm of water (Table 3). The mean lengths of the urethral pressure profiles were 29 and 30 mm respectively.

The ice-water test revealed contractions $> 15$ cm of water in 4 of the 10 patients on whom it was performed; 3 of them were also found to have significant uninhibited neobladder contractions during cystometry and a fourth showed only diminished compliance. None of the patients with total substitution could sense the iced water, whereas all patients in the augmentation group did so.

**Table 3** Urodynamic Characteristics of the Detubularised Right Colonic Neobladder

| | *Augmentation Mean (range)* | *Total substitution Mean (range)* |
|---|---|---|
| Peak flow rate (ml/s) | 32 (15–45) | 21 (13–30) |
| Maximum closure pressure (cm of water) | 44 (27–66) | 70 (26–147) |
| Length of pressure profile (mm) | 30 (24–40) | 29 (24–40) |

Most of our patients accepted the right colonic neobladder for urinary diversion and classified the results as "good" or "very good". Only 1 patient was dissatisfied because of incontinence by day, which disturbed his work. The other patient with day-time incontinence felt it to be so mild that it did not disturb him and he required only 1 pad/day.

## Discussion

These results confirm that a detubularised right colonic segment provides a low pressure reservoir with adequate functional capacity.

Almost all segments of the bowel have been used for bladder reconstruction, and each has its enthusiasts and opponents based on anatomical and urodynamic considerations (Camey and LeDuc, 1979; Thueroff *et al.*, 1985; Goldwasser *et al.*, 1986; Light and Engelmann, 1986; Reddy *et al.* 1987; Melchior *et al.*, 1988). It has recently been realised, however, that only operations involving detubularisation will benefit from the consequent alterations in geometry, accommodation, compliance and contractility that reduce harmful contractions and at the same time yield the largest capacity from the shortest segment of bowel (Goldwasser *et al.*, 1987; Hinman, 1988). We selected the right colonic segment because of the relatively easy surgical procedures involved, good blood supply to the anastomosis and simplicity in deciding the intestinal length. This is in accordance with the results of the present series, which showed no significant peri-operative complications. Construction of a neobladder from the colon avoids further resection of the terminal ileum, which is of importance in the absorption of vitamin B12, as compared with reservoirs constructed from the ileum plus caecum (Thueroff *et al.*, 1985; Light and Engelmann, 1986; Reddy *et al.*, 1987). The colon has the advantage of allowing safe, easy submucosal reimplantation of the ureters, thus preventing reflux. However, 2 patients developed an obstruction in the ureterointestinal anastomosis, possibly because of excessive scarring in the tunnel area. The stenosis occurred more than 1 year after the operation, and this underlines the importance of careful follow-up.

The reservoir capacities observed here were within the upper limits of the normal bladder and exceeded those of ileal neobladders (Roehrborn *et al.*, 1987; Hautmann *et al.*, 1988; Melchior *et al.*, 1988). Similar capacities have been reported after replacement with an ileocolonic pouch (Light and Engelmann, 1986; Thueroff *et al.*, 1986). Compliance was also similar to that reported for ileal neobladders (Melchior *et al.*, 1988). Although most of our patients showed contractions exceeding 15 cm of water in urodynamic evaluation, this did not occur at low volumes and the amplitude was usually low. Equally high maximum reservoir pressures have been measured in ileocolonic reservoirs (Thueroff *et al.*, 1986). Thus a neobladder constructed from a detubularised right colonic segment fulfils the criteria for a low pressure reservoir as well as do techniques which incorporate the ileum into the right colon either as a patch or the ileum alone (Thueroff *et al.*, 1985; Light and Engelmann, 1986; Roehrborn *et al.*, 1987; Hautman *et al.*, 1988; Melchior *et al.*, 1988).

The intraluminal pressure of the neobladder did not exceed the maximum urethral closure pressure. It was higher in the total substitution group than in the females of the augmentation group, while the length of the urethral pressure profile was approximately the same. Despite this, the females had better night-time continence that the males. Nocturnal incontinence seems to be common to all types of bladder substitute, a possible cause being the loss of sacral route reflex activity after total cystectomy (Thueroff *et al.*, 1986; Roehrborn *et al.*, 1987; Melchior *et al.*, 1988; Månsson and Colleen, 1990). The females with an intact bladder neck after augmentation probably maintained this reflex activity, which helps to preserve continence during sleep. The 2 patients with total substitution were suffering from mild day-time incontinence after cystoprostatectomy; in 1 case this was not manifested until the patient returned to work, which involved climbing and lifting. These patients could be treated with an alloplastic sphincter prosthesis (Reddy *et al.*, 1987).

The voiding frequency was very close to that of normal subjects, with low residual urine and a high flow rate. Only 1 patient was unable to empty his total substitution neobladder sufficiently, requiring intermittent self-catheterisation. The majority of the 12 patients treated with total bladder substitution gradually regained sensations of fullness closely simulating those of a normal bladder. Similar findings have been reported in patients with sigmoid bladders (Koskela and Kontturi, 1982) and ileal neobladders (Hautmann *et al.*, 1988; Melchior *et al.* 1988). They probably learned to interpret intestinal symptoms as signs of a full neobladder (Melchior *et al.*, 1988). None of these patients was able to feel the iced water in the cooling test, however. One completely lacked any recognisable sensation of bladder fullness and avoided overdistension by voiding at regular intervals. The sensation from a full neobladder is often too weak to awaken the patient at night and this is another reason for nocturnal incontinence. This could be avoided if the patient could wake up for micturition every 2 to 3 hours (Melchior *et al.*, 1988; Månsson and Colleen, 1990).

Acid urine causes excessive water secretion in the ileal neobladder, which can result in dehydration and desiccation if the urine is not alkalised (Melchior *et al.*, 1988). All patients with intestinal material interposed in the urinary tract, if studied carefully, can be shown to absorb excessive chloride and hydrogen ions (McDougal, 1986). The major factors that determine the degree of metabolic disturbance are the total surface area of the reabsorbing mucosa and the state of the patient's renal function (Goldwasser *et al.*, 1986). Only 1 of our patients (6%) was acidotic and continuously in need of alkalising drugs and this is much less than the 50% reported with ileal neobladders (Melchior *et al.*, 1988). This acidosis may have been partly due to the fact that the patient had previously undergone total gastrectomy on account of ventricular cancer. Therefore, although determination of serum electrolytes and pH at regular intervals is important in all urinary reservoir patients, it seems that disturbances in electrolyte balance are not as common with right colonic neobladders as with ileal ones.

Bladder replacement with a detubularised right colonic segment is easier to perform than most comparable procedures; the ensuing urodynamic properties and patient satisfaction, which depend on urinary continence, micturition intervals and post-operative complications, are equal to those achieved with more complicated neobladders constructed from the ileum or the right colon and ileum. This operation can therefore be recommended as one possibility for bladder replacement. More patients and longer follow-up periods are required for proper evaluation of its real efficacy and the fate of the upper urinary tract.

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# Detubularisation in Cystoplasty: Clinical Review

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Summary—Cystoplasty using a detubularised bowel segment is preferable to using a tubularised length of intestine. This has been shown experimentally to result in a reduction in the contractility of the neobladder, although contractions are not completely abolished. Incontinence, especially nocturnal, may still be a problem. Assessment of renal function has shown a marked incidence of upper tract dysfunction despite detubularisation. All patients remain at risk of upper tract obstruction following cystoplasty. Because bowel contraction waves are brought on by distension, it may be possible either to postpone or to prevent the onset of contractions by avoiding an excessive build-up of bladder volume. Clean intermittent self-catheterisation is an efficient means of emptying the bladder, although sphincter rebalancing may also be required.

Bladder augmentation or substitution by cystoplasty using bowel segments is increasing in popularity (Goldwasser and Webster, 1986), but the long-term effects are not known.

In a previous animal study (Cheng and Whitfield, 1990), we showed that detubularisation resulted in a reduction in contractility, although this was not completely abolished. Contractions are undesirable not only because they may provoke day-time or nocturnal incontinence, but also because the pressure rises may be transmitted to the upper urinary tract and result in an obstructive uropathy or nephropathy (Weiss, 1987).

In order to study the clincial relevance of these experimental findings we followed up a group of cystoplasty patients and assessed their renal and bladder function.

## Patients and Methods

All patients who had undergone a cystoplasty between 1981 and 1989 were reviewed. Symptoms of day-time and nocturnal frequency, continence and the presence or absence of mucus were recorded.

Renal function was assessed by the measurement of urea, creatinine and electrolytes, blood gas analysis, creatinine clearance and isotope renography. Bladder function was assessed by urine culture and videourodynamics.

## Results

The series comprised 23 patients, 7 male and 16 female, with an age range of 23 to 79 years. They were followed up for a mean duration of 19.2 months after cystoplasty (range 1.5–52).

Indications for surgery included interstitial cystitis in 7 patients, bladder malignancy in 6, bladder instability in 5, bladder neuropathy in 3 and post-irradiation frequency in 2.

All patients had a detubularised cystoplasty; 17 had an ileocystoplasty, 10 of which were in the form of a clam ileocystoplasty, and the rest had some form of a cup-patch, "S", "U" or "W" ileocystoplasty; 6 patients had an ileocaecocystoplasty.

Additional procedures performed post-operatively included clean intermittent self-catheterisation (CISC) in 11 patients to facilitate bladder emptying. Sphincter rebalancing was carried out in 3 patients, which included urethrotomy, urethral dilatation and bladder neck incision. In 1 patient a Brantley Scott prosthesis had been implanted prior to cystoplasty.

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### *Complications*

Early complications included blockage of the urethral catheter in 2 patients, anastomotic leakage requiring laparotomy in 1 and depression in another.

The commonest late complication was difficulty in voiding or incomplete bladder emptying and this was present in 12 patients. Almost invariably, abdominal straining was required to void. Nocturnal incontinence was noted in 7 patients and this was associated with either a low compliant neobladder or with hyperactivity. Mucus was noted in the urine by all patients and caused acute urinary retention in 4; these 4 patients required hospitalisation and urethral catheterisation. Recurrent urinary infection was seen in 3 patients, 2 of whom were using intermittent self-catheterisation, and long-term, low dose antibiotics were required by these patients. "Diverticularisation" of the bowel component of the cystoplasty was noted during videourodynamics in 2 patients (Fig. 1); in both cases a clam ileocystoplasty had been performed. Two patients developed intestinal adhesions but both had received irradiation in the past. Bladder calculi developed in 1 patient who failed to empty her bladder adequately (Fig. 2) and cystoscopic litholapaxy was required.

Two patients died, the first of unknown cause 17 months after surgery. She had both interstitial cystitis and transitional cell carcinoma, the latter being localised to the dome of the bladder. Clinically, she had no metastases and post mortem examination was refused. The second patient had a cystoprostatectomy for oat cell carcinoma of the bladder. He developed a recurrence despite chemotherapy and died 11 months after surgery. Post mortem examination was not carried out.

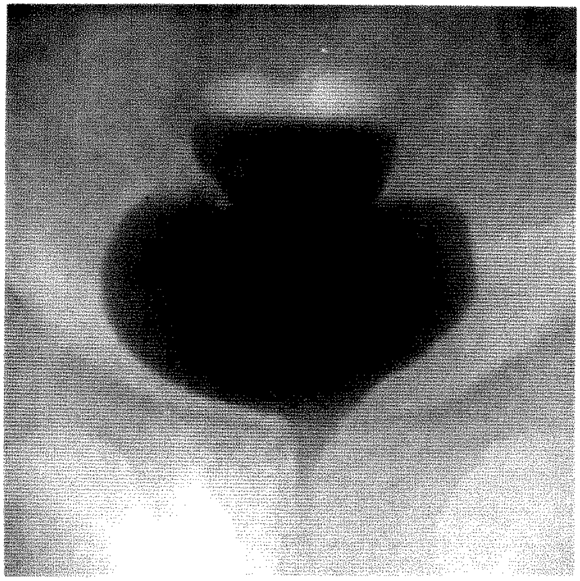

**Fig. 1** "Diverticularisation" in an ileocystoplasty.

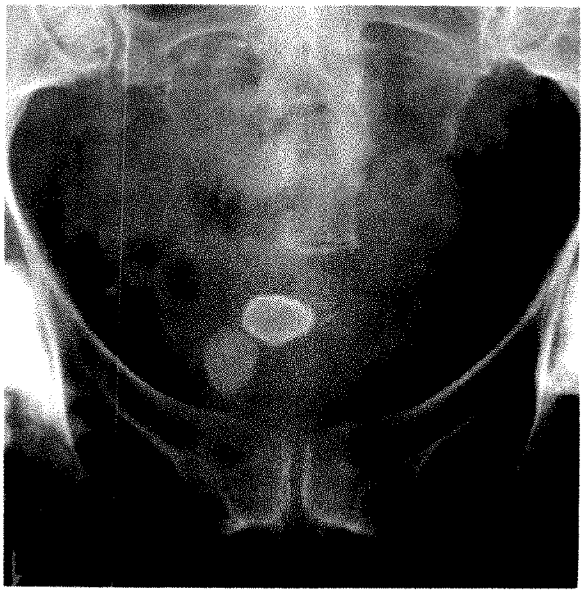

**Fig. 2** Bladder calculi in an ileocaecocystoplasty.

### *Renal Function*

Urea and electrolytes were normal in all patients except 1 who had a slightly raised chloride level of 108 mmol/l (upper limit of normal 105 mmol/l). Blood gas analyses were carried out in 19 patients and were abnormal in 2 who showed a mild acidosis but had otherwise normal renal function. Creatinine clearance was estimated in 15 patients with a mean result of 72 ml/min (range 4–159).

In all, 22 patients underwent isotope renography, representing a total of 44 renal units (Tables 1 and 2). Pelvic retention (whole kidney transit time index > 170 s) was seen in 21 renal units. Comparing ileocystoplasty and ileocaecocystoplasty, 50% of the former group had pelvic retention (16/32 renal units) and 42% of the ileocaecocystoplasty group had pelvic retention (5/12). Obstructive nephropathy (parenchymal transit time index > 156 s) was seen in only 1 renal unit in a patient with a detubularised ileocystoplasty (1/32); vesicoureteric reflux was also present in this kidney but the contralateral kidney, which did not show reflux, had no obstructive nephropathy.

**Table 1** Isotope Renography in Detubularised Ileocystoplasty

| | *PTTI (s)* | | *WTTI (s)* | |
|---|---|---|---|---|
| *Patients* | *Right kidney* | *Left kidney* | *Right kidney* | *Left kidney* |
| MB | 82 | 100 | 543 | 279 |
| EL | 58 | 127 | 193 | 216 |
| HM | 83 | 119 | 179 | 157 |
| AH | 49 | 26 | 45 | 83 |
| VJ | 49 | 124 | 105 | 618 |
| JR | 75 | 72 | 312 | 273 |
| PG | 59 | 72 | 156 | 186 |
| CD | 71 | 98 | 319 | 138 |
| BH | 63 | 96 | 123 | 166 |
| JH | 58 | 45 | 185 | 75 |
| EB | 57 | 45 | 351 | 182 |
| JW | 103 | 161 | 467 | 614 |
| HR | 54 | 53 | 149 | 125 |
| RRe | 45 | 47 | 136 | 203 |
| EC | 65 | 78 | 109 | 93 |

PTTI (Parenchymal transit time index) (normal < 156 s).
WTTI (Whole kidney transit time index) (normal < 170 s)

**Table 2** Isotope Renography in Detubularised Ileocaecocystoplasty

| | *PTTI (s)* | | *WTTI (s)* | |
|---|---|---|---|---|
| *Patients* | *Right kidney* | *Left kidney* | *Right kidney* | *Left kidney* |
| FS | 88 | 80 | 100 | 120 |
| CB | 145 | 134 | 238 | 211 |
| TB | 51 | 70 | 159 | 205 |
| EM | 95 | 150 | 140 | 412 |
| RRu | 75 | 75 | 75 | 101 |
| AW | 48 | 73 | 124 | 242 |

PTTI (Parenchymal transit time index) (normal < 156 s).
WTTI (Whole kidney transit time index) (normal < 170 s).

### *Bladder Function*

Urine culture showed a significant growth in 14 patients; 8 patients had a mixed growth, 3 cultures grew coliforms and the rest grew *Proteus mirabilis*, non-haemolytic *Streptococcus* and *Bacillus*. Four of these patients were using CISC.

Videourodynamics showed that vesicoureteric reflux was present in 1 or both kidneys in 5 patients, none of whom had had reimplantation of the ureters. Instability in the form of regular contractions and a gradual rise in baseline pressure was seen in 6 patients; 3 of these had undergone a detubularised ileocaecocystoplasty and the other 3 a detubularised ileocystoplasty. In 4 of these 6 urodynamic investigations, contraction waves did not begin until a bladder volume ranging from 300 to 700 ml had been reached and contractions continued to increase in magnitude with further filling (Fig. 3). The other 2 patients showed contractions at the beginning of bladder filling.

Individual urodynamic results are listed in Tables 3 and 4. The mean capacity in the ileocaecocystoplasty group was 787 ml compared with 510 ml in the ileocystoplasty group. There was no statistically significant difference between these results (Student's *t* test). The mean residual volume for ileocaecocystoplasty was 148 ml compared with 163 ml for ileocystoplasty. Ten patients had residual volumes > 100 ml (range 120–770). Taking a normal compliance as more than a 500 ml increase in

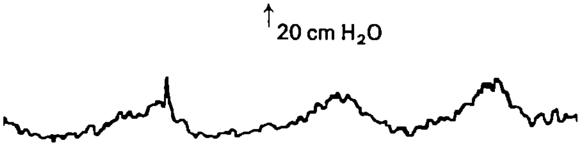

**Fig. 3** Urodynamic tracing showing detrusor pressure waves.

**Table 3** Urodynamic Results in Detubularised Ileocystoplasty

| *Patients* | *Bladder capacity (ml)* | *Residual volume (ml)* | *End-filling pressure (cm $H_2O$)* | *Compliance* (ml/cm $H_2O$)* |
|---|---|---|---|---|
| MB | 630 | 440 | 10 | 63 |
| ML | 300 | 10 | 2 | 150 |
| HM | 700 | 0 | 15 | 47 |
| AH | 380 | 130 | 40 | 10 |
| VJ | 900 | 710 | 21 | 43 |
| JR | 100 | 3 | 70 | 1 |
| PG | 325 | 0 | 21 | 16 |
| CD† | 1350 | 25 | 34 | 40 |
| BH | 560 | 75 | 12 | 47 |
| ED | 175 | 0 | 30 | 6 |
| JH | 370 | 5 | 10 | 37 |
| EB | 350 | 250 | 28 | 12 |
| JW† | 285 | 200 | 40 | 7 |
| MS | 750 | 170 | 30 | 25 |
| HR | 700 | 425 | 0 | — |
| RRe | 500 | 330 | 0 | — |
| EC | 300 | 0 | 0 | — |

* Normal compliance > 33 ml/cm $H_2O$.
† Unstable neobladder.
— Infinity.

**Table 4** Urodynamic Results in Detubularised Ileocaecocystoplasty

| *Patients* | *Bladder capacity (ml)* | *Residual volume (ml)* | *End-filling pressure ($cm\ H_2O$)* | *Compliance* ($ml/cm\ H_2O$)* |
|---|---|---|---|---|
| FS† | 1500 | 0 | 36 | 42 |
| CB | 150 | 0 | 20 | 8 |
| TB† | 800 | 0 | 34 | 24 |
| EM† | 475 | 120 | 32 | 15 |
| RRu | 200 | 0 | 0 | — |
| AW† | 1600 | 770 | 18 | 89 |

* Normal compliance > 33 ml/cm $H_2O$.
† Unstable neobladder.
— Infinity.

volume for a pressure rise of 15 cm $H_2O$ (< 33 ml/cm $H_2O$), 7 ileocystoplasties (7/17) showed reduced compliance and 3 ileocaecocystoplasties (3/6) had reduced compliance. Of the 10 patients with reduced compliance, the reasons for surgery included unstable bladder, interstitial cystitis, post-irradiation, neuropathy and malignancy. With the exception of bladder malignancy, most of the remaining patients (6/10) had no part of the diseased bladder excised.

## Discussion

The detubularised intestinal segment is now generally preferred to the tubularised version (Goldwasser and Webster, 1986). When a tubularised loop of bowel segment is distended with fluid in a neobladder, sustained contractions occur and can reach pressures of 100 cm $H_2O$ or more in both large and small intestine (Kock, 1969; Light and Engelmann, 1985). These pressure waves in the neobladder may be sufficiently high to overcome the urethral closing pressure (40 cm $H_2O$) and result in urinary incontinence (Studer *et al.*, 1989). Nocturnal incontinence is more common than daytime incontinence (Lytton and Green, 1989). Excision of the trigone and bladder neck may reduce the sensation of fullness and urge to void, thus allowing the bladder capacity to be exceeded without awakening the patient (Whitmore and Gittes, 1983; Roehrborn *et al.*, 1987). The decrease in urethral closing pressure, relaxation of pelvic floor muscles during sleep (Steven *et al.*, 1986) and failure of the sphincter to increase in tone in response to the contractions in the neobladder during sleep (Jakobsen *et al.*, 1987), plus the fact that the total 24-h urinary output in patients with intestinal urinary reservoirs exceeds that of normal individuals, may all contribute to nocturnal incontinence following cystoplasty (Åkerlund *et al.*, 1989).

A second effect of contractility is that the increase in intravesical pressure, without a concomitant increase in intra-abdominal pressure, may lead to a reduction in the cuff closing pressure of an artificial urinary sphincter and result in urinary leakage (Light and Engelmann, 1985).

More significant is the possible effect that contractility may have on the upper tract. Bladder distension and a raised intravesical pressure may obstruct the ureter (Gill and Curtis, 1977), partly because stretching of the trigonal musculature or ureter by bladder distension may obstruct the intramural ureter (Tanagho *et al.*, 1965; Weiss, 1987).

Detubularisation, or the longitudinal incision of the smooth muscles of bowel segments, interrupts the directional peristalsis and results in a low pressure, highly compliant and large capacity bladder (Kock, 1969). A single longitudinal incision along the intestinal wall will not abolish contractions because most of the smooth muscle fibres remain intact. By continuing to fill and distend the detubularised segment, the contraction waves may return. This could explain why some workers claim that a certain detubularisation technique is superior in eliminating contractility, or that adaptation of the neobladder or reservior occurs with time (Hedlund *et al.*, 1984; Berglund *et al.*, 1987). It may be that the activity in the bowel wall has not been eliminated but merely postponed, and when filling is adequate, contraction waves can reappear. In the present study, contractions were seen in 6 patients, in 4 of them the contractions began at bladder volumes of 300 to 700 ml.

Isotope renography revealed pelvic retention in 48% of the renal units investigated. Most of our patients had a normal serum biochemistry and blood gas analysis, despite the high incidence of abnormal findings on isotope renography. Isotope renography is the most sensitive indicator of renal dysfunction and should be employed in the post-operative assessment of cystoplasty patients.

All patients with residual volumes > 100 ml were taught clean intermittent self-catheterisation and the many benefits of this technique are well documented (Lapides *et al.*, 1976). Since peristalsis in the intestinal wall can be brought on by dilatation or stretching (Connell, 1986), it may be possible either to delay or to prevent the onset of these contractions by preventing an excessive build-up of bladder volume. By so doing, the possible adverse effects of contraction waves on the upper tracts may be avoided. This may prove to be an additional value of CISC not previously described.

In conclusion all patients who have had cystoplasties must be followed up for life. Investigations should include assessment of renal function with blood test, blood gas analysis and isotope renography. Intravenous urography alone is both inadequate and inaccurate. Bladder function should be studied using urine culture and urodynamic studies. If a small residual volume is revealed (< 100 ml), the patient should be encouraged to void regularly to prevent excessive build-up of bladder volume. If a large residual volume (> 100 ml) is present, intermittent self-catheterisation should be taught. Alternatively, sphincter rebalancing may be performed. Intermittent self-catheterisation appears to be a satisfactory form of improving bladder emptying.

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# Chronic Abacterial Prostatitis and Hyperthermia
## A Possible New Treatment?

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Summary—A group of 45 patients with chronic abacterial prostatitis or prostatodynia underwent 6 weekly, 1-hour sessions of local deep microwave hyperthermia (42.5 ± 0.5°C) to the prostate.

All patients had a long history of symptoms typical of the condition. They all failed to respond to a variety of conventional treatments administered over several years by various specialists. Each patient served as his own control before and after the hyperthermic treatment. The results of this study are encouraging: 25% showed a sustained and complete loss of symptoms and 50% had a partial response; the remaining 25% reported no improvement. These results open up new possibilities in the treatment of this condition, which has so far responded poorly to conventional therapy.

"Chronic prostatitis is ill-understood, difficult to diagnose, and often unresponsive to treatment" (Thin and Simmons, 1983a). According to Stamey (1981), the incidence of non-bacterial prostatitis is unknown, but it is an everyday clinical experience and is more common than true bacterial prostatitis.

Patients with non-bacterial prostatitis complain of similar symptoms to those found in patients with bacterial prostatitis, such as low back or perineal discomfort, intermittent burning on urination, some degree of urinary urgency and frequency, and painful ejaculation (Orland *et al.*, 1985); however, no pathogenic organism can be identified.

Hyperthermia, defined as elevation of tissue temperature to 41 to 44°C, is becoming a recognised modality in the treatment of cancer, both alone and in combination with other established treatments (Johnson and Pavelec, 1973; Overgaard, 1978; Field and Bleehan, 1979; Hahn, 1979; von Ardenne, 1980; Sterzer, 1982). In previous reports (Yerushalmi *et al.*, 1982; Servadio and Leib, 1989), we presented our initial observations on the treatment of prostatic cancer with local deep microwave hyperthermia (LDMWH). Later, with the co-operation of Biodan Ltd (Rehovot, Israel), we developed improved apparatus which was initially tested in animal studies (Leib *et al.*, 1986) and subsequently used in the treatment of humans, with encouraging results (Servadio *et al.*, 1986, 1987, 1989).

Non-bacterial prostatitis is difficult to manage effectively with treatments such as anti-bacterial therapy, anti-inflammatory agents or periodic prostatic massage. The present study reports our experience with non-bacterial prostatitis patients treated by hyperthermia.

### Patients and Methods

The series included 45 patients with chronic abacterial prostatitis (negative expressed prostatic secretion (EPS) and semen culture) ranging in age from 31 to 74 years (average 44.3); they were evaluated and later underwent hyperthermic treatment. The patients had an average symptomatic period of 7.6 years (range 6 months–26 years) prior to undergoing hyperthermia and various medications (on average 6 per patient) had been of little help. Surgical treatment, such as transurethral resection (TUR) of the prostate in 4 elderly patients,

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also failed to eliminate the problem and symptoms recurred in 4 to 6 weeks.

To assess the efficacy of hyperthermia, the patients' symptoms were divided into 2 major groups: subjective and objective (Tables 1 and 2). To quantify the subjective answers obtained from the patients, a self-explanatory questionnaire was designed. This questionnaire was completed by the patient himself before the first hyperthermia session, after 3 to 4 sessions, 1 week after the last session, and 3, 6 and 12 months thereafter. Long-term follow-up was also conducted. Pain, degree of complaints and disturbances as well as other factors were quantified in a 1 (worst) to 9 (healthy) scale (Table 2).

To exclude bacterial prostatitis, urine cultures ($VB_1$, $VB_2$ and $VB_3$), EPS and semen cultures were performed. The patient population was not differentiated on the basis of those suffering from either non-bacterial prostatitis or from prostatodynia as classified by Stamey (1980).

The following objective tests were performed: blood chemistry and count, uroflowmetry, residual urine measurements and transrectal ultrasound (TRUS) scan (Bruel & Kerr B-type scanner model No. 1849). The first 12 patients in the group had also had a prostate biopsy before treatment with a repeat biopsy 1 month after completion of treatment (Table 1).

For 6 weeks prior to the administration of hyperthermia, each patient received doxycycline (100 mg/day). Only after the recurrence of symptoms (1–2 months later) was the patient assessed for hyperthermic treatment and this was then started within 1 week. The few patients whose symptoms disappeared (and did not recur) were excluded from the study. Doxycycline (a tetracycline antibiotic) was selected as many studies had reported good results with tetracycline antibiotics (Milingos *et al.*, 1983; Thin and Simmons, 1983b).

**Table 2** Subjective Analysis and Timing
A self-explanatory questionnaire on the following symptoms

| *Symptoms* | *Timing* |
|---|---|
| Urgency | Before treatment |
| Frequency | End of treatment |
| Dysuria | 1 } After treatment (months) |
| Nocturia | 3 } After treatment (months) |
| Low back pain | 6 } After treatment (months) |
| Perineal pain | 12 } After treatment (months) |
| Low abdominal pain | Every 6 months |
| Muscle pain | Thereafter |
| Ejaculation pain | |
| | *Range—Score* |
| | 1–9 |
| | 1—worst situation. |
| | 9—best situation |

The Prostathermer D99$^{(TM)}$ was used to heat the prostate. This consists of a specially designed rectal probe, a microwave power source of 915 MHz, a device for cooling the rectal wall, several temperature monitors placed both in the rectal wall and the prostatic urethra and a computerised automatic control and data collecting system.

Treatment consisted of 6 weekly sessions, each lasting 1 h and performed on an ambulatory basis. Neither anaesthesia nor analgesia was needed.

## Results

All 45 patients were followed up for 3 to 62 months (mean 38.5). Two patients were later lost to follow-up (1 with coronary insufficiency and the other with a brain tumour); 22 patients were satisfied and wished no further treatment. The other 23 (although some showed partial improvement) required com-

**Table 1** Objective, Analysis and Timing

| | | | *After treatment (months)* | | | |
|---|---|---|---|---|---|---|
| *Analysis* | *Before treatment* | *End of treatment* | *1* | *3* | *6* | *12* |
| Blood chemistry count | + | + | + | + | + | + |
| EPS and $VB_1$, $VB_2$, $VB_3$ | + | | + | + | + | + |
| Spermatogram | + | | | + | | + |
| Sperm culture | + | | | + | | + |
| TRUS prostate | + | + | | + | | + |
| Digital examination *per rectum* | + | + | + | + | + | + |
| Uroflowmetry and residual urine | + | | + | + | + | + |
| *Biopsy of prostate | + | | + | | | |

* Only the first 12 patients

plementary treatment as antibiotics, vitamins or alpha-blockers (13), tranquillisers (4) and endoscopic treatment (3). In only 5 of the 12 patients who underwent a needle biopsy of the prostate did the histology reveal definite inflammatory infiltration changes. Control biopsies following hyperthermic treatment showed almost complete disappearance of these changes. The uroflowmetry, residual urine and size of the prostate did not reveal any significant changes on transrectal ultrasound scan.

Subjective improvement was divided into 3 categories: complete (25%), partial (50%) with a mean duration of 25.6 and 17.5 months respectively, and no improvement in 25% (Table 4); 28 patients complained of discomfort and pain in the lower abdomen, lower back and perineal area. The average rate of improvement in these symptoms was 44% with a mean duration of 22.6 months. Twelve patients who complained of dysuria and a burning sensation on micturition improved by an average of 60% over a period of 30.8 months; 19 patients who complained of urgency and frequency improved by an average of 45% over a mean period of 22.3 months. Six patients with recurrent urinary tract infection improved by an average of 97.5% over a mean period of 22 months.

Since most of the patients with chronic prostatitis were young and also had infertility problems, we monitored variations in sperm analysis before and after hyperthermic treatment. No change for the worse was noted. On the contrary, 5 pregnancies followed hyperthermic treatment in this group, the result of a clear improvement in sperm analysis.

**Table 3** General Results

| | *None** | *Partial†* | *Complete‡* |
|---|---|---|---|
| Improvement | 11 | 21 | 11 |
| Mean duration (months) | 25.6 | 17.5 | 34 |
| | (4–55) | (3–59) | (12–56) |
| Mean improvement (%) | 47.5 | | |
| | (0–100; n=43) | | |

*None 0–10% improvement
†Partial 20–75% improvement.
‡Complete 80–100% improvement

## Discussion

The results of this study are based mainly on subjective symptoms. Chronic prostatitis is a difficult and controversial clinical entity, but all such patients—whether bacterial, non-bacterial or with prostatodynia—appear to share common aetiological factors other than the few bacteria which might be found in the EPS. Recognising the problem of accurate diagnosis because of urethral contamination of the EPS, Mardh and Colleen (1975) compared the bacteriological findings in non-acute prostatitis patients with those in 20 healthy, normal volunteers. Their findings indicated that there was no difference in the incidence of bacteria in the EPS between the 2 groups.

Some aetiological factors other than bacteria may be involved in chronic prostatitis, *e.g.* intraprostatic reflux (Kirby *et al.*, 1982), the host's local defence mechanism, the hormonal milieu of the prostate and the biological behaviour of the infecting organisms (Gunn and Gould, 1956; Kaplan *et al.*, 1983).

Each patient served as his own control and, before entering the study, each was treated with doxycycline. We adopted the "effective" tetracycline therapy of Thin and Simmons (1986b) as a baseline and only those patients who failed to respond to doxycycline and relapsed early (less than 2 months) were eligible to receive hyperthermia. The histological improvement in 5 patients is also of objective value. The results following long-term follow-up (Table 3) reveal new perspectives in the therapeutic approach to this disease. Heat may be useful on its own but may also be helpful when combined with antibiotic or anti-inflammatory drugs, since it alters their pharmacokinetic proper-

**Table 4** Subjective Improvement According to Symptoms

| *Symptoms* | *No* | *Improvement* (%)* | *Average improvement (%)* | *Follow-up (months)* | *Average length of follow-up (months)* |
|---|---|---|---|---|---|
| Low abdominal, back, perineal pain and discomfort | 28 | 0–98 | 44 | 3–59 | 22.6 |
| Dysuria and burning on micturition | 12 | 0–100 | 59.5 | 9–56 | 30.8 |
| Urgency and frequency | 19 | 0–100 | 44.5 | 3–56 | 22.3 |
| Urinary tract infection | 6 | 90–100 | 97.5 | 3–56 | 22 |

*The 0% included patients without improvement (almost the entire group) ties. The effect of hyperthermia on fertility is also interesting and this is currently being investigated.

We conclude that local hyperthermia can be regarded as a safe, easily applied modality for the treatment of chronic abacterial prostatitis. It brings about a marked relief of symptoms, does not harm and may even improve male fertility potential. This modality offers new possibilities of therapy in this controversial and poorly understood, yet common, clinical condition.

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# Severe Hepatocellular Dysfunction following Cyproterone Acetate Therapy

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Summary—Cyproterone acetate (CPA) is a widely used drug in the treatment of advanced prostatic carcinoma. Although it is generally well tolerated, liver toxicity has been recognised as a complication of long-term use. We report 3 patients with severe hepatocellular damage due to CPA therapy, 2 with fatal fulminant hepatitis.

Since the reports by Huggins and Hodges (1941) and Herbst (1941) that the growth of prostatic carcinoma was promoted by testosterone and that castration or oestrogen therapy could inhibit this growth, adjuvant therapy for advanced prostatic carcinoma has become commonplace. Over recent years cyproterone acetate (Cyprostat, Schering Health Care Ltd) has become widely used in such circumstances. CPA exerts a direct anti-androgenic effect on the tumour and its metastases, and additionally has a negative feedback effect on the hypothalamic receptors, thus leading to a reduction in gonadotrophin release and hence diminished testicular androgen production.

It is generally a well tolerated drug, but among the more severe side effects is hepatocellular toxicity, which has been reported in 6 patients. In 2 of these, the findings were of acute hepatitis (Meijers *et al.* 1986), whilst Lévesque *et al.* (1989) reported a case of fulminant hepatitis which resulted in fatal liver failure.

We report a further 3 cases of severe hepatocellular damage due to CPA therapy: 2 patients with fatal fulminant hepatitis and 1 with acute hepatitis which occurred in the period January to June 1989.

## Case Reports

*Case 1.* A 72-year-old man was admitted with a 3-week history of deepening, non-pruritic jaundice, pale stools and dark urine. Moderately differentiated, invasive carcinoma of the prostate had been diagnosed in 1987 and treated by transurethral resection of the prostate (TURP) and CPA 100 mg *tds*, liver function tests (LFTs) being normal at that time. Physical examination revealed no other abnormality apart from pronounced jaundice. LFTs on admission were markedly deranged: total bilirubin 326 μmol/l (normal 1–20 μmol/l); alkaline phosphatase (ALP) 218 iu/l (6–130 iu/l); aspartate transaminase (AST) 254 iu/l (<45 iu/l); gamma glutaryl transferase (GGT) 612 iu/l (<65 iu/l). Prothrombin time was prolonged at 22 s (13–16.5 s). Serological markers for hepatitis A, B, cytomegalovirus and herpes viruses were negative. Antibodies to smooth muscle, nuclei and mitochondria were negative. Ultrasonography revealed no hepatomegaly or hepatic metastases. Liver biopsy confirmed acute hepatitis.

CPA was discontinued immediately and a hepatic failure regime was instituted with gradual improvement in his general condition. After 6 weeks the total bilirubin had fallen by 50% but liver enzymes were still grossly elevated. Treatment with steroids was therefore commenced with prednisolone 30 mg daily. By a further 6 weeks the patient was fully recovered with normal LFTs.

*Case 2.* A 65-year-old man was admitted with a 6-week history of progressive jaundice. Poorly differentiated prostatic carcinoma with bone metastases had been diagnosed 12 months earlier and treatment with CPA 100 mg *tds* was commenced. LFTs at that time had shown no abnormality. Apart from profound jaundice, physical examination was unremarkable, with no evidence of hepatomegaly. LFTs revealed a total bilirubin of 177 μmol/l; ALP 252 iu/l; AST 377 iu/l; GGT 512 iu/l. Serological markers for hepatitis A, B, cytomegalovirus and herpes viruses were negative. Antibodies to smooth muscle, nuclei and mitochondria were negative. Ultrasound revealed no hepatic abnormality.

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CPA therapy was stopped. Despite treatment of his hepatic failure, the patient continued to deteriorate and succumbed to hepato-renal failure 11 days after admission. Post mortem examination confirmed the presence of metastatic prostatic carcinoma, although there were no deposits in the liver. Death was due to fulminant hepatitis.

*Case 3.* An 83-year-old man was admitted with a 1-week history of right hypochondrial pain, diminished appetite, weight loss and jaundice with passage of pale stools and dark urine. Localised moderately differentiated carcinoma of the prostate had been found 3 years earlier following admission with acute urinary retention and treatment by TURP. He remained well for 21 months, when CPA 100 mg *tds* was commenced for local extension of the prostatic malignancy. At this time LFTs were within the normal range. On physical examination deep jaundice and cachexia were the sole positive findings. LFTs on admission were abnormal with a total bilirubin of 281 μmol/l; ALP 79 iu/l; AST 155 iu/l, GGT 65 iu/l. Serological markers for hepatitis A, B, cytomegalovirus and herpes viruses were negative. Antibodies to smooth muscle, nuclei and mitochondria were negative. Ultrasonography showed gall stones but no abnormality of the liver.

A hepatic failure regime was implemented and CPA was withdrawn immediately. Despite active treatment, his general condition continued to deteriorate and he died 6 days after admission. Post mortem examination confirmed extensive prostatic carcinoma with death due to fulminant hepatitis, but with no evidence of metastatic carcinoma in the liver.

## Discussion

Liver damage due to CPA is a rare complication of its prolonged use, only 6 cases having previously been reported. In our 3 cases of severe hepatotoxicity CPA may be directly implicated, since all investigations for other possible causes of hepatic dysfunction were negative and none of the patients were on any other potentially hepatotoxic drugs at the time of illness.

The mechanism of CPA-induced liver damage is not understood. The absence of clinical and biochemical manifestations of hypersensitivity, both in our cases and in those previously reported in the literature, suggests that CPA-induced hepatic dysfunction is due either to direct or to reactive metabolite toxicity.

Although the risk of hepatic damage with CPA therapy is small, all patients on this drug should have liver function closely monitored. We recommend that prior to commencing this treatment, all patients have confirmation of normal liver function. Thereafter, they should undergo regular checks of LFTs (as recommended by the manufacturer) in order to detect signs of liver failure at an early stage. Signs of hepatic dysfunction should be managed by immediate withdrawal of CPA and switching to an alternative non-hepatotoxic therapy such as orchiectomy or an LHRH analogue.

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# Toxicity Study of First and Second Generation Hydrogel-coated Latex Urinary Catheters

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Summary—The hydrogel-coated urinary catheter is a novel formulation in which the coating hydrogel polymer is claimed to reduce the level of cytotoxicity frequently associated with the use of latex catheters. This study was undertaken to measure cytotoxicity using *in vivo* techniques.

Twelve first generation and 5 second generation hydrogel-coated latex catheters were evaluated *in vivo* using canine urethras. The results showed all catheters to cause minimal inflammatory changes of the urethral mucosa (toxicity score 0–1.2/6).

In 1982 an "epidemic" of urethral strictures in patients catheterised with a brand of latex catheter was reported (Ruutu *et al.*, 1982). Studies confirmed that the catheters contained substances that were toxic to cells in culture and focused attention on the potential toxic effects of urinary catheters in general (Graham *et al.*, 1983). It was recognised that in addition to this recent "epidemic" the literature contained many reports of urethritis and stricture formation related to the use of catheters, the earliest being by Browne (1893).

The National Biological Standards Laboratory in Canberra was the first testing authority to respond to the clinical and experimental evidence of toxicity, and introduced a standard for urinary catheters incorporating a toxicity test which all catheters marketed in Australia were required to pass (Standards Association of Australia, 1984). This standard has recently been adjusted to impose more stringent toxicity requirements, with the result that the catheter manufacturers have been forced to withdraw substandard catheters. Evidence now exists that only non-toxic catheters should be used (Nacey *et al.*, 1985a and b).

Recognition of this problem has resulted in a decline in use of the uncoated latex catheter and a preference for silicone or teflon-coated catheters which tend to be non-toxic owing to the protective surface coating. Pure silicone catheters are also favoured because of their low or nil toxicity (Nacey *et al.*, 1986). The hydrogel-coated catheter is a new type which is claimed to be biocompatible and non-toxic to tissue (C. R. Bard Inc.) and consists of a latex substrate coated with a special hydrophilic polymer which forms part of the class of compounds known as "hydrogels". Chemically, the coating material is a hydrophilic polyurethane. Such materials are relatively inert and biocompatible. They have been used extensively in other medical applications such as contact lenses, synthetic cartilages and drug delivery systems.

The aim of this study was to assess the hydrogel-coated catheter with respect to its toxic potential.

## Materials and Methods

The catheters used in this study were 8 F Bard hydrogel-coated latex urinary catheters. The first generation catheters are coated with a simple hydrogel and are marketed in the UK and USA as the "Biocath". The second generation catheters have a modified hydrogel coating. In the USA these are marketed as the "Lubricath" but in the UK the term "Biocath" has been retained. Twelve first generation and 5 second generation catheters were assessed in the animal model.

This study was approved by the Ethical Commit-

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tee for Animal Experimentation of the Wellington School of Medicine.

Seventeen juvenile to adult male dogs of unknown age were used in the assessment of catheter toxicity. All were obtained from a commercial dog breeder who routinely provided dogs for scientific investigation. They were housed individually and provided with regular dry feed and water.

Under general anaesthesia, a urethrostomy was constructed in the proximal portion of the penile urethra according to the method of Nacey *et al.* (1985a). A 5-cm length of catheter was then inserted through the urethrostomy into the penile urethra and sutured in place. The catheters were left indwelling for 24 h, after which the dogs were killed and the urethra prepared and sectioned following the method previously described. The sections from each urethra were examined under light microscopy and each was graded according to the degree of epithelial ulceration and inflammatory infiltrate using a modification of the grading system described by Nacey *et al.* (1985a) (Table 1). The scores obtained from the assessment of the degree of ulceration and inflammation were then summed to provide a total histopathological score. A mean score was then derived from all 5 sections taken from each urethra examined.

## Results

Sections taken from the urethras of all 17 dogs showed either an absence of epithelial ulceration (6 dogs) or minimal ulceration in no more than 1 of 5 levels taken from each urethra (6 dogs). There was no evidence of inflammation, either in the epithelium or underlying supporting stroma in the urethras of 2 dogs. The remaining dogs showed minimal superficial active inflammation (grade I) in 2 to 5 sections.

**Table 1** Histopathological Toxicity Grading System (modified from Nacey *et al.* (1985a))

| | Score |
|---|---|
| *Degree of ulceration* | |
| i. No ulceration | 0 |
| ii. 20% of epithelium ulceration | 1 |
| iii. 20–50% of epithelium ulcerated | 2 |
| iv. 50% of epithelium ulcerated | 3 |
| *Inflammation* | |
| 1. No inflammation | 0 |
| 2. Occasional lymphocytes, plasma cells and/or neutrophils within epithelium and stroma | 1 |
| 3. Moderate numbers of lymphocytes, plasma cells and/or neutrophils within epithelium and stroma | 2 |
| 4. Dense infiltration of lymphocytes, plasma cell and neutrophils. The epithelium, where present, contains numerous neutrophils and there is an associated acute inflammatory exudate | 3 |

The mean histopathological toxicity score derived from all 17 dogs used in this study was 0.75 (Table 2).

**Table 2** Mean Histopathological Toxicity Score for First and Second Generation Hydrogel-coated Catheters. (The mean histopathological toxicity score for all catheters is 0.75 (scale 0–6))

| *First generation* | | *Second generation* | |
|---|---|---|---|
| *Dog identification* | *Score* | *Dog identification* | *Score* |
| A | 0.4 | M | 0.4 |
| B | 1.2 | N | 0.6 |
| C | 1.0 | O | 0.6 |
| D | 0.6 | P | 1.0 |
| E | 0.8 | Q | 1.0 |
| F | 0.4 | | |
| G | 1.2 | | |
| H | 1.2 | | |
| I | 0.0 | | |
| J | 0.0 | | |
| K | 1.0 | | |
| L | 1.2 | | |

## Discussion

It was not until 1982 that the stricture "epidemic" focused attention on the toxicity of catheters (Ruutu *et al.*, 1982; Sutherland *et al.*, 1982; Syme, 1982; Wesley-James, 1982). It was apparent that there was very little regulatory control over the manufacture or quality of catheters. Standards specifically for catheters did exist but these were mainly concerned with their mechanical and structural properties (British Standards Institution, 1981a and b). In Australia and the United Kingdom standards have now been produced which incorporate guidelines on catheter toxicity (Standards Association of Australia, 1984).

The importance of the Australian and British guidelines appears to have been recognised by many clinicians and most catheter manufacturers, with the result that increased varieties of non-toxic catheters are becoming available for use. With so many different catheters available, the importance of toxicity testing and the publication of the test results cannot be over-emphasised.

Many catheters are made using a latex substrate with either silicone or teflon coatings in the belief that this will eliminate toxicity. It is known that in many cases the coating is an unreliable barrier to the diffusion of toxic products from the underlying latex, and that as a rule the coating either dissolves or disintegrates (Cox, 1987). Many manufacturers prefer to market "pure" silicone catheters in order to avoid the problems that surface coatings may have.

The physiological benefits of hydrophilic polymers have been recognised and incorporated into major health care products, soft contract lenses being the most familiar. Hydrophilic polymers [hydrogels] swell on contact with water and retain a significant proportion of water within the polymeric structure. The polymer becomes softer, more flexible and has a characteristic slippery surface. When applied as a coating to urinary catheters this provides a low coefficient of friction leading to easy catheter insertion (C. R. Bard Inc.).

The Bard "Biocath" and "Lubricath" catheters employ a hydrogel coating over a latex substrate and the results from this study confirm that the catheters cause minimal urethral inflammation. This implies either that the hydrogel coating prevents diffusion of products from the underlying substrate or that the underlying substrate is itself non-toxic. Scanning electron microscopic studies show that the hydrogel coating remains largely intact during use and that only minute areas of denudation are seen (Cox, 1987). It would therefore appear that the hydrogel may afford protection to the adjacent urethral epithelium while the catheter is in use.

In a previous study using an identical animal model, various other types of coated and uncoated catheters were assessed (Nacey *et al.*, 1985a). This has allowed a useful comparison between these and hydrogel-coated catheters. The mean toxicity score for the hydrogel-coated catheter was 0.75 (toxicity scale 0–6), which is a very similar result to that obtained for pure silicone catheters (mean toxicity scores 1.2, 1.4). The low tissue reaction caused by the hydrogel-coated catheters, when combined with their comparative low cost and excellent surface qualities, makes then an attractive alternative to other types of coated catheter for clinical use.

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# Recurrent Haemospermia—Underlying Urogenital Anomalies and Efficacy of Imaging Procedures

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Summary—Recurrent haemospermia is often regarded as "essential". Following routine diagnostic procedures, we found an associated factor in 54 of 72 patients (75%). With one exception (prostatic carcinoma), the benign character of the disease was confirmed. Urogenital infection was the most frequent concomitant finding (50%); in 26 men chronic prostatitis was diagnosed. Other disorders such as hypertension and coagulation disorders played a minor role. Additional investigation of the prostate gland and seminal vesicles by transrectal prostatic ultrasonography revealed persistent asymmetry of the latter glands as the main finding in 20 men (28%). In every case seminal vesicle carcinoma was excluded; haemorrhage due to cystic distension, inflammatory lesions or ductal obstruction was associated in all cases with congenital abnormalities, chronic urogenital infection, coagulation disorders or hypertension.

Haemospermia means the presence of blood in the semen and is associated mainly with urogenital infections, especially prostatitis and vesiculitis (Yada, 1963; Yu *et al.*, 1977). Fletcher *et al.* (1981) found that urogenital inflammation was a cause of haemospermia in 67% of patients. In some cases, disorders of the coagulation system (Leary and Aguilo, 1974) and severe hypertension (Kreutz and Bandhauer, 1978) were regarded as general causes of bleeding. Haemospermia has also been associated with unexpected neoplastic disease of the lower urinary tract, especially carcinoma of the prostate (Leary and Aguilo, 1974) and, less frequently, seminal vesicle carcinoma (Benson *et al.*, 1984).

Nevertheless, in some patients the origin of haemospermia remains obscure and the symptom is described as "essential" (Leary and Aguilo, 1974; Tolley and Castro, 1975; Kreutz and Bandhauer, 1975; Yu *et al.*, 1977). This may be because, apart from some cases of venous bleeding from the prostatic plexus that can be confirmed by urethrocystoscopy (Fletcher *et al.*, 1981), the investigators are unable to identify the site of the bleeding. Although older vesiculographic studies (Yada, 1963) suggest involvement of the seminal vesicles, new data are not available.

The development of transrectal prostatic ultrasonography (TPS) has facilitated visualisation of anatomical abnormalities of these glands (Benson *et al.*, 1984; Colpi *et al.*, 1985; Roehrborn *et al.*, 1986; Kawahara *et al.*, 1988). In this study, every patient underwent TPS, in addition to clinical and microbiological investigations.

## Patients and Methods

Between March 1982 and December 1988, a study was made of 72 patients (mean age 38 years, range 19–72) who complained of more than one bout of haemospermia before attending our prostatitis outpatient department. All underwent a standardised diagnostic procedure (Table 1). Their medical history was recorded with particular emphasis on duration of symptoms, urogenital infections and other diseases.

The search for urogenital infection followed standard procedures using the "4-specimen-technique" (Brunner *et al.*, 1983) and ejaculate analysis (Weidner *et al.*, 1985). Microbiological investiga-

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**Table 1** Diagnostic Procedure

Medical history
Physical examination
"4-specimen-technique"
Semen analysis
Transrectal ultrasonography
Urethrocystoscopy*
CT scan of prostate gland and seminal vesicles†
Ultrasonically guided biopsy†

*In all cases without evidence of urogenital infection.
†In all cases with unilateral enlargement of the seminal vesicles without evidence of urogenital infection and ultrasonic suspicion of solid mass.

tions included quantitative determination of common bacteria, mycoplasma, yeasts and *Trichomonas vaginalis* in all urine specimens, expressed prostatic secretions (EPS) and ejaculate. A urethral swab was cultured for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Three urine portions were cultured for mycobacteria.

Tests for urethritis and prostatitis included leucocyte analysis of urethral or prostatic secretions.

In addition to the routine examination of ejaculate, semen was analysed with regard to erythrocytes and numbers of Papanicolaou stained leucocytes (Weidner *et al.*, 1985). At a later stage, peroxidase-positive leucocytes (World Health Organisation, 1987) were measured in all men without symptomatic urogenital infection.

The diagnosis of urethritis was based on a history of urethral discharge; cytologically, the detection of ≥ 15 leucocytes/400 × in the sediment of a single urine specimen indicated chronic urethritis.

Epididymitis was diagnosed clinically by a swollen, tender epididymis.

Prostatitis was diagnosed in patients with increased numbers of leucocytes in the EPS (≥ 10 PML/1000 × (HPF)) and/or urine after prostatic massage (≥ 10/400 × (LPF)); chronic bacterial prostatitis (CBP) was diagnosed by a typical number of common bacteria in the "4-specimen-technique" (Brunner and Weidner, 1985).

*C. trachomatis*, detected in urethral swabs, was assumed to be the aetiological agent in cases of urethritis and epididymitis. A similar finding in cases of prostatitis meant it was classified as "non-bacterial".

In semen, $\geq 10^3$ PAP stained leucocytes/ml suggested infection and $\geq 10^3$ peroxidase positive leucocytes/ml confirmed it (Comhaire *et al.*, 1980; Weidner *et al.*, 1985; World Health Organisation, 1987).

Pathological bacteriospermia was diagnosed if the number of bacteria or *Ureaplasma* exceeded $10^3$ cfu/ml ejaculate (Weidner *et al.*, 1985; World Health Organisation, 1987).

After exclusion of symptomatic urogenital infection, silent infection was diagnosed in the case of bacteriospermia and increased numbers of leucocytes (Comhaire *et al.*, 1980; World Health Organisation, 1987).

Transrectal prostatic ultrasonography was performed in the supine position using a fixed-image instrument with grey scale imaging and a focusing probe of 3.5 MHz (Bruel/Kjaer, DK) (Weidner *et al.*, 1985). Examinations were carried out after sexual abstinence for at least 3 days directly after prostatic massage and after emptying the bladder. Ultrasonic tomograms were made at 1-cm intervals. After examining the prostate for calcifications and cystic abnormalities, the transverse section with the greatest seminal vesicle diameter was used for analysis. If the vesicles were asymmetrical, the glands were studied separately. Sonographic findings were reassessed 1 week later followed by a pelvic CT scan. If ultrasound suggested a solid mass, the diagnosis was clarified by ultrasonically guided biopsy.

## Results

Sixty of the 72 patients (90%) complained of recurrent bouts of haemospermia over periods ranging from 1 month to more than 2 years. The remainder complained of haemospermia of less than a month's duration. In 62 patients (86%), haemospermia was the main symptom and erythrocytes were detected in the ejaculate on their first visit. Other symptoms included dysuria (17 patients), testicular pain (5), perineal pain (17) and prostatism (28). Haematuria was present in only 2 patients.

Urogenital infections were found in 36 men (50%) (Table 2). With 3 exceptions, these patients were under 40 years of age. Symptomatic urethritis, epididymitis and prostatitis were diagnosed in 33 men. Non-bacterial prostatitis was the most common lower urogenital infection and *E. coli* and *C. trachomatis* were the most common micro-organisms. Of the 19 patients with non-bacterial prostatitis, the diagnosis was made in 9 cases solely on the basis of increased numbers of leucocytes in prostatic secretions; in a further 6 men in this group, urethral swabs from the urethra were positive for *C. trachomatis*; in 4 men large numbers of *Ureaplasma* were isolated from the semen. Silent

**Table 2** Evidence of Urogenital Infections

| | |
|---|---|
| Chronic urethritis | 2 |
| (positive for *C trachomatis**) | (1) |
| Epididymitis | 5 |
| (high numbers of *E coli* in semen) | (2) |
| (positive for *C. trachomatis**) | (1) |
| Chronic bacterial prostatitis | 7 |
| (due to *E. coli*) | (5) |
| (due to *E. faecalis*) | (2) |
| Non-bacterial prostatitis | 19 |
| (positive for *C trachomatis**) | (6) |
| (high numbers of *U. urealyticum* in semen) | (4) |
| Silent urogenital infection | 3 |
| (due to *E. coli*) | (2) |
| (due to *U. urealyticum*) | (1) |

*positive urethral swabs

urogenital infection, based on bacteriospermia and increased leucocytes in the semen but no evidence of urethritis, prostatitis or epididymitis, was detected in only 3 men. Tuberculosis was excluded in every case.

General and local disorders usually associated with haemospermia were found in 18 men (25%) (Table 3). Either severe hypertension or coagulation disorders were presumed to be involved in 10 patients. Local urethral bleeding was verified in 6 men, in 1 of whom digital suspicion of prostatic carcinoma was confirmed by biopsy. In a further 2 men, the diagnosis of cystic fibrosis with azoospermia and palpable cystic seminal vesicles indicated bleeding from these glands.

Transrectal prostatic ultrasonography (Table 4) demonstrated, in addition to the sonographic feature of adenoma (18 men), prostatic calcification in 5 patients with chronic bacterial prostatitis and cystic lesions in 4. In one of the patients with recurrent epididymitis, a central cystic sonographic abnormality (Fig. 1A) was confirmed as a utricular cyst by urethrocystoscopy and retrograde filling (Fig. 1B). Imaging of the seminal vesicles demonstrated persistent asymmetry in 20 men; in only 8 of these did one vesicle become palpable. In 17 patients, TPS revealed a distorted cavum on one side without inner echoes (Fig. 2) but, at the same time, the sharp circumference of the contralateral smaller gland did not indicate any anomalies. Clinically, 8 of these men suffered from prostatitis, 2 from epididymitis, 2 from cystic fibrosis, 1 from von Willebrand Jürgens syndrome and 3 from severe hypertension. In 2 cases the asymmetry was due to cystic enlargement of one gland together with other urogenital anomalies. In 1 case, TPS demonstrated areas of increased and decreased echo intensity together with an irregular shape (Fig. 3A). CT scan confirmed a heavily enlarged seminal vesicle with cystic inclusions (Fig. 3B). In another case, the abnormalities of the vesicle were sustained by ectopic ureter drainage into the gland (Fig. 3C). In a further patient, cystic deformation of the seminal vesicle coincided with agenesis of the ipsilateral kidney. Both patients suffered from recurrent prostato-urethritis and epididymitis with persistent bouts of haemospermia.

**Table 3** General and Local Diseases Associated with Haemospermia

| | |
|---|---|
| *General* | |
| Severe hypertension | 5 |
| Coagulation disorders (Marcumar treatment (4) von Willebrand-Jürgens syndrome (1)) | 5 |
| Cystic fibrosis (and azoospermia) | 2 |
| *Local* | |
| Benign prostatic hyperplasia with bleeding veins at the bladder neck | 3 |
| Perineal trauma (with urethral bleeding) | 2 |
| Prostatic carcinoma with haematuria | 1 |

**Table 4** Transrectal Prostatic Ultrasonographic Results and Concomitant Findings

| *Results* | | *Comment* |
|---|---|---|
| Prostatic calcifications | 5 | CBP in all cases |
| Cystic lesions | 4 | |
| (utricular cyst) | (1) | Epididymitis |
| Asymmetry of seminal vesicles | 20 | |
| | (17) | With prostatitis (8)<br>Epididymitis (2)<br>Cystic fibrosis (2)<br>Coagulation disorder (1)<br>Hypertension (3) |
| (Seminal vesicle cysts) | (2) | With prostatitis and epididymitis |
| (Haematoma) | (1) | Hypertension |

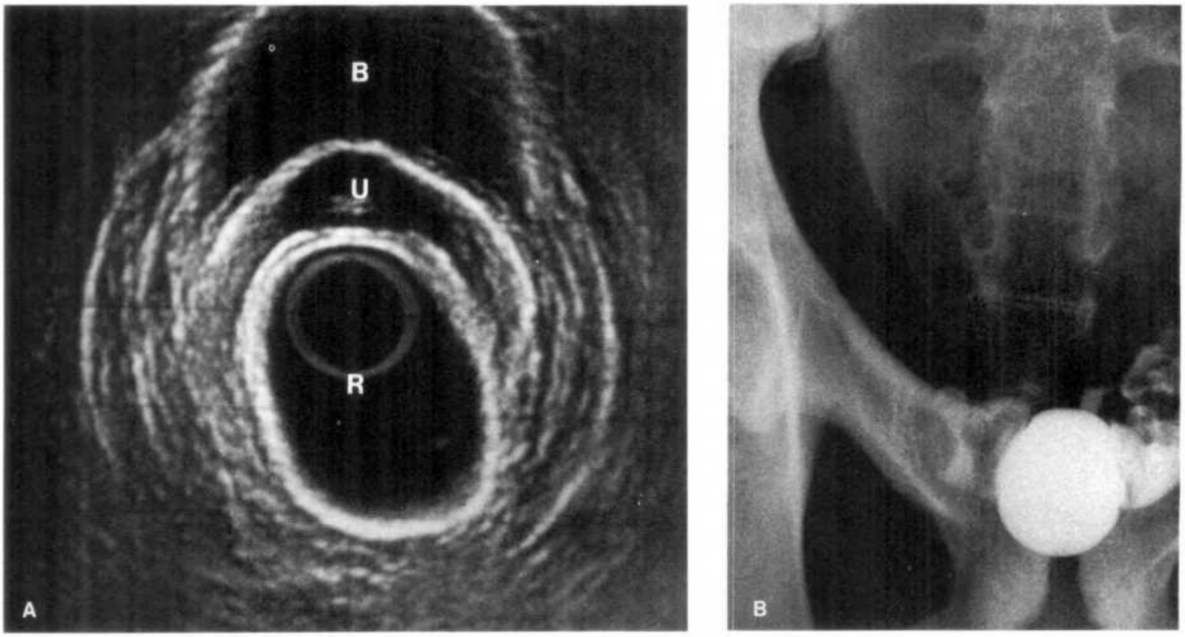

**Fig. 1** (A) TPS shows enlarged cystic utricle (U) between bladder (B) and rectum (R). (B) Endoscopic filling of utricular orifice.

In the remaining patient, who had hypertension, asymmetry on TPS was first thought to be due to a tumour of the left vesicle (Fig. 4A) and this could not be ruled out by CT scan (Fig. 4B). Malignant changes were excluded following ultrasonically guided biopsy, which revealed an old haematoma in the left gland.

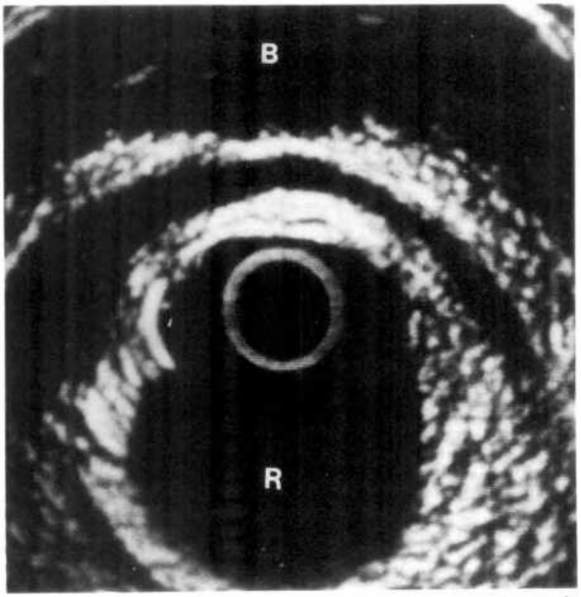

**Fig. 2** TPS demonstrates asymmetrical appearance of seminal vesicles (B: bladder. R: rectum).

## Discussion

Haemospermia is mainly associated with lower urogenital infections, especially with prostatovesiculitis (Yada, 1963; Yu *et al.*, 1977; Fletcher *et al.*, 1981). This type of infection, predominantly chronic prostatitis, was diagnosed in 50% of our patients and although tuberculosis is often regarded as a major cause (Yu *et al.*, 1977), we excluded it in every case. With the exception of 7 men suffering from urethritis or epididymitis, the symptoms indicated prostatitis. In fact, in men under 40 years of age, both bacterial and non-bacterial prostatitis were very common. In the 19 patients with non-bacterial prostatitis, the diagnosis was first established on the evidence of increased numbers of leucocytes in prostatic secretions, thus emphasising that prostatic massage should be included in the diagnostic procedures. In 10 of these men, uncommon bacteria, such as *C. trachomatis* or *Ureaplasma*, were isolated, indicating that they might be involved in the inflammatory process, although their aetiological role is still debatable (Brunner and Weidner, 1985). Unfortunately, the incidence of prostatitis has not been investigated adequately in this connection. Fletcher *et al.* (1981), who reported a thorough search for factors linked to haemospermia, did not perform prostatic massage in all cases. Subclinical or "silent" infections, based upon bacteriospermia and increased leucocyte

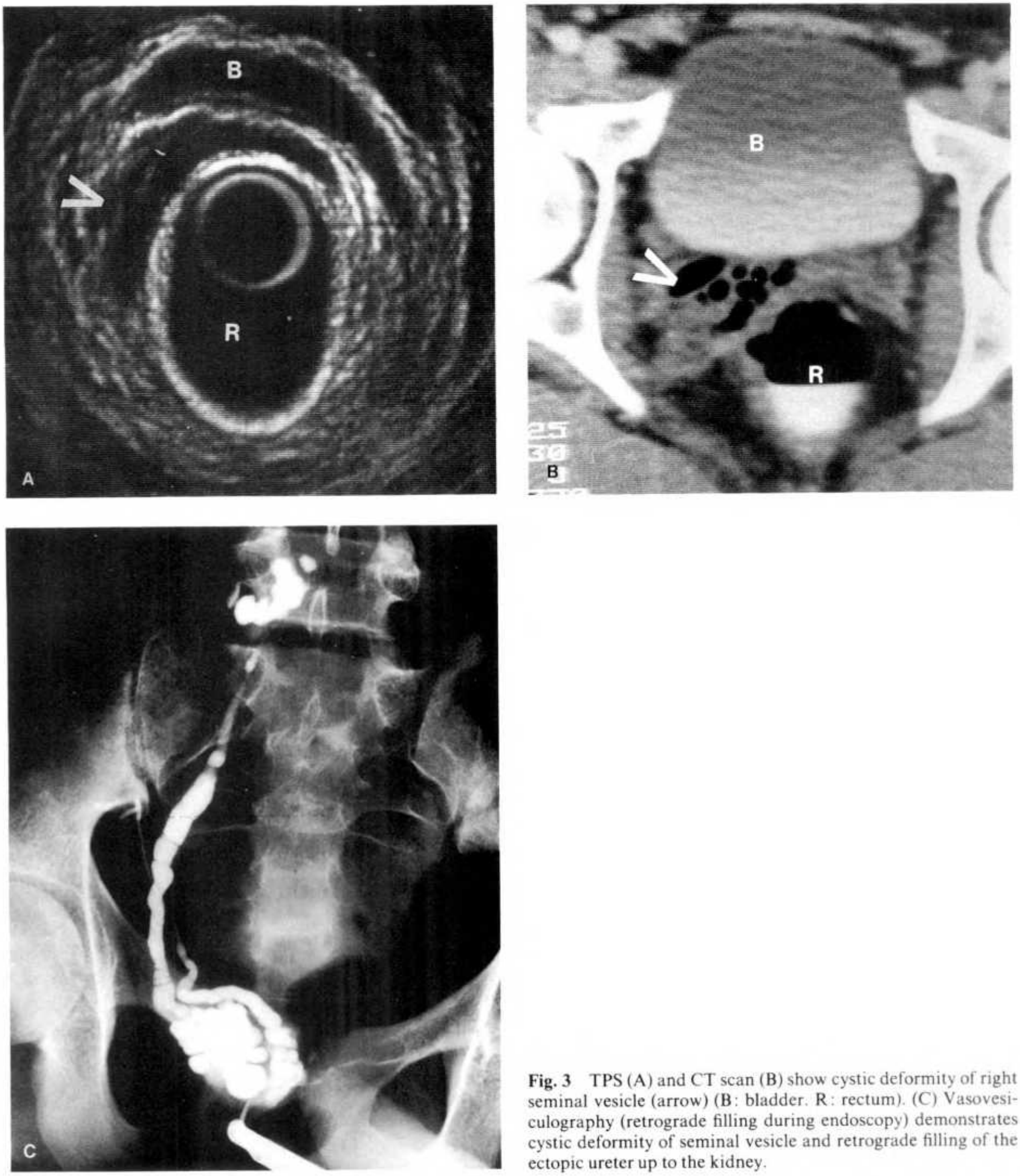

**Fig. 3** TPS (A) and CT scan (B) show cystic deformity of right seminal vesicle (arrow) (B: bladder. R: rectum). (C) Vasovesiculography (retrograde filling during endoscopy) demonstrates cystic deformity of seminal vesicle and retrograde filling of the ectopic ureter up to the kidney.

numbers in the semen (World Health Organisation, 1987), were extremely rare and comparable data are not available. Only Yada (1963) produced evidence of leucocytes in smears from his patients. Nevertheless, a reassessment of these findings is worthwhile, since modern techniques for identifying leucocytes and leucocyte subpopulations are readily available (El-Demiry *et al.*, 1986) and they facilitate the search for silent infections of the accessory glands (Comhaire *et al.*, 1980).

Other general and local diseases associated with haemospermia play a minor role. Severe hyperten-

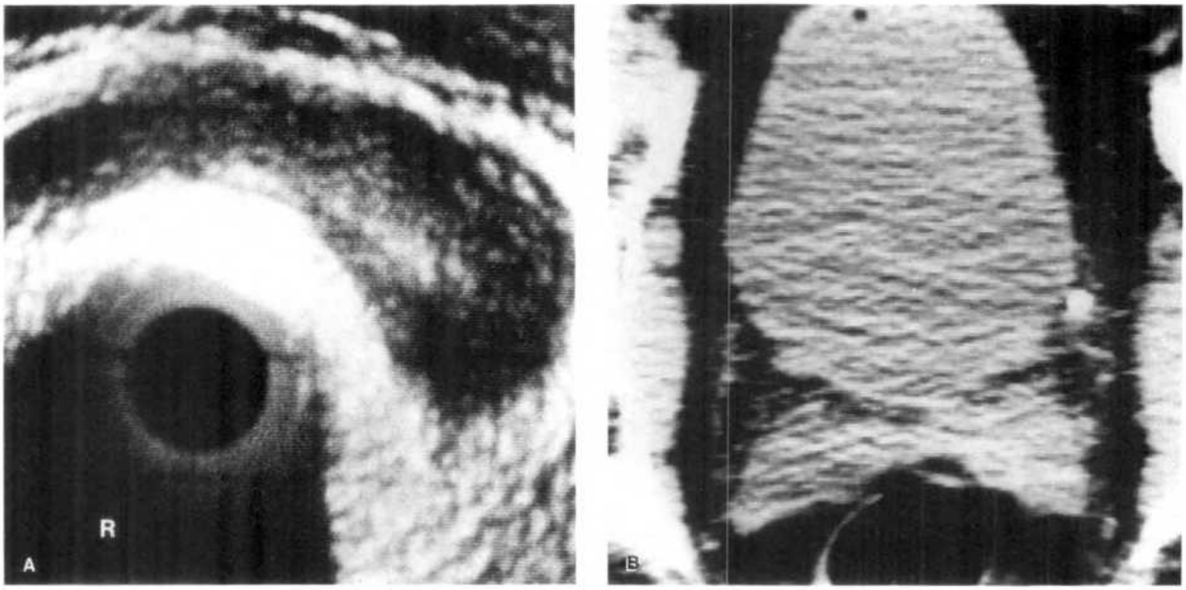

**Fig. 4** TPS (A) and CT scan (B) show a possible solid mass in the left seminal vesicle (R: rectum).

sion (5 patients) and coagulation disorders (5) are accepted as sustaining bleeding in the ejaculatory pathway (Leary and Aguilo, 1974). The incidence of local urethral bleeding has also been verified in this study, *e.g.* after perineal trauma, in some cases combined with benign prostatic hyperplasia. As in the case of the man with prostatic carcinoma, these data compare well with other findings (Fletcher *et al.*, 1981).

In cases of cystic abnormalities of the prostate or seminal vesicles, the suggestion of an association between disturbed drainage and haemospermia, either due to direct mucosal inflammatory lesion or cystic extension (Yada, 1963; Leary and Aguilo, 1974; van Poppel *et al.*, 1983; Roehrborn *et al.*, 1986) seems well accepted.

The TPS findings of asymmetry of the seminal vesicles are worthy of discussion. Yada (1963) demonstrated asymmetry of both glands by vesiculography in 27.2% of his patients with haemospermia. He attributed this to cystic distension following inflammatory ductal obstruction. In the present study, TPS revealed asymmetrical seminal glands in 20 of 72 men, *i.e.* 27%. What are the possible causes of this asymmetry? We know that the volume of both glands is mainly influenced by the period of sexual abstinence (Jiménez-Cruz *et al.*, 1982; Colpi *et al.*, 1985) and it is also related to the size of the prostate (Tanahashi *et al.*, 1975). However, both factors cannot influence the size of only one gland, especially if the secretory status (Jiménez-Cruz *et al.*, 1982) has been standardised by a 3-day abstinence period. Asymmetry may depend upon a number of factors, *e.g.* rare genuine hypoplasia (Colpi *et al.*, 1985), cystic malformation due to congenital anomalies (Roehrborn *et al.*, 1986) and, most often, infectious abnormalities (Tanahashi *et al.*, 1975; Jiménez-Cruz *et al.*, 1982; Colpi *et al.*, 1985). In the case of infection, the abnormalities are possibly caused by vesicular involvement in lower urogenital infection, especially prostatitis (Jiménez-Cruz *et al.*, 1982; Colpi *et al.*, 1985), either by enlargement due to inflammatory ductal obstruction (Yada, 1963) or by the shrinking of one infected gland (Baert *et al.*, 1986) simulating contralateral dilatation. Of 20 patients with persistent asymmetry of the glands in the present study, evidence of non-bacterial prostatitis in 8 or epididymitis in 2 suggested vesiculitis as a probable cause of bleeding.

In the other patients, the impression of dilatation of one gland was associated with severe hypertension or coagulation disorders. In these men, recurrent haemorrhage through sexual intercourse was thought to sustain haemospermia (Kreutz and Bandhauer, 1978). In one man, the swelling of one vesicle was shown by biopsy to be a haematoma. In the other cases, cystic lesions associated with congenital disorders such as cystic fibrosis, which is often linked with urogenital malformation (Kaplan *et al.*, 1968), or seminal cysts with upper urinary tract malformation (Roehrborn *et al.*, 1986), explain the symptom either by inflammatory or secretory obstruction and distension of the cystic walls and vessels.

Our findings confirm the generally benign nature of haemospermia (Leary and Aguilo, 1974; Fletcher *et al.*, 1981) and that it is mainly associated with urogenital infections, especially chronic prostatitis. The only patient with prostatic carcinoma was the eldest in our series and the malignancy was detected early by palpation and biopsy. Changes in the seminal vesicles, especially persistent asymmetry, were confirmed as benign and caused by the involvement of the glands in urogenital inflammation or as congenital cystic development. When vesicular carcinoma is suspected, ultrasonically guided biopsy facilitates prompt histological assessment (Kawahara *et al.*, 1988), thus avoiding the need for further imaging techniques which should be limited to special indications, *i.e.* when other malformations of the upper urinary tract are suspected (Roehrborn *et al.*, 1986).

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PAEDIATRIC UROLOGY

# Complications of Transurethral Electro-incision of Posterior Urethral Valves

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Summary—The development of dense urethral strictures following transurethral resection of posterior urethral valves is a well known complication, especially in the neonate. In 85 boys with posterior urethral valves no strictures were found during follow-up. Urinary incontinence associated with transurethral incision occurred in 3 patients and a small urethral diverticulum was found in 1. The complication rate associated with the transurethral incision itself was 5%. Our technique for transurethral incision of posterior urethral valves is described.

Advances in prenatal ultrasound have increased the number of boys with posterior urethral valves being detected *in utero* or shortly after birth. Consequently the need for a safe method of treating the valves at an early age has become greater. The initial treatment in most cases is transurethral resection or fulguration of the valves. The development of urethral strictures and incontinence after valve resection have been described by Crooks (1982) and Williams *et al.* (1973). All boys treated in this unit between 1971 and 1985 have been evaluated retrospectively to determine the risk of stricture formation and urinary incontinence associated with transurethral resection of posterior urethral valves.

## Patients and Methods

Between 1971 and 1985, 85 boys were referred for primary treatment of posterior urethral valves. Those who were referred for further treatment after undergoing primary valve ablation elsewhere were excluded from the study. Between 1971 and 1979 a loop electrode was used for transurethral electroresection of the valves in 50 boys. Between 1979 and 1985 a hook electrode was used for transurethral electro-incision in 35 boys (Fig.).

The primary treatment of boys with posterior urethral valves is transurethral bladder drainage (Scott, 1985). In very small infants a 5 F feeding tube is used. After stabilisation of the patient a voiding cystourethrogram (VCUG) is performed, usually after 4 or 5 days, to confirm the diagnosis and to rule out vesicoureteric reflux. Initial serum creatinine, clinical condition and the condition of the upper urinary tract all determine the course of action. In some patients ablation of the valves alone may be sufficient; in others a vesicostomy or high diversion may be necessary. Transurethral valve incision in the very young can be performed after a couple of days. An 8 F resectoscope can be used transurethrally. Three days before introduction of an 8 F instrument we replace a 5 F feeding tube with a 6 F feeding tube and after another 2 days we use an 8 F tube. In most children even a 10 F tube can then be easily introduced. After valve incision or resection an 8 F Foley catheter is inserted and then removed 3 to 5 days later, depending on the condition of the patient. Before removal of the catheter another voiding cystogram is performed. In no case was general anaesthesia used to perform a VCUG. Only in patients with initial urinary tract infection or septicaemia were antibiotics continued during the resection. In all other cases antibiotic treatment commenced the day before removal of the catheter and continued for as long as was deemed necessary, taking into account upper urinary tract abnormalities and urine cultures.

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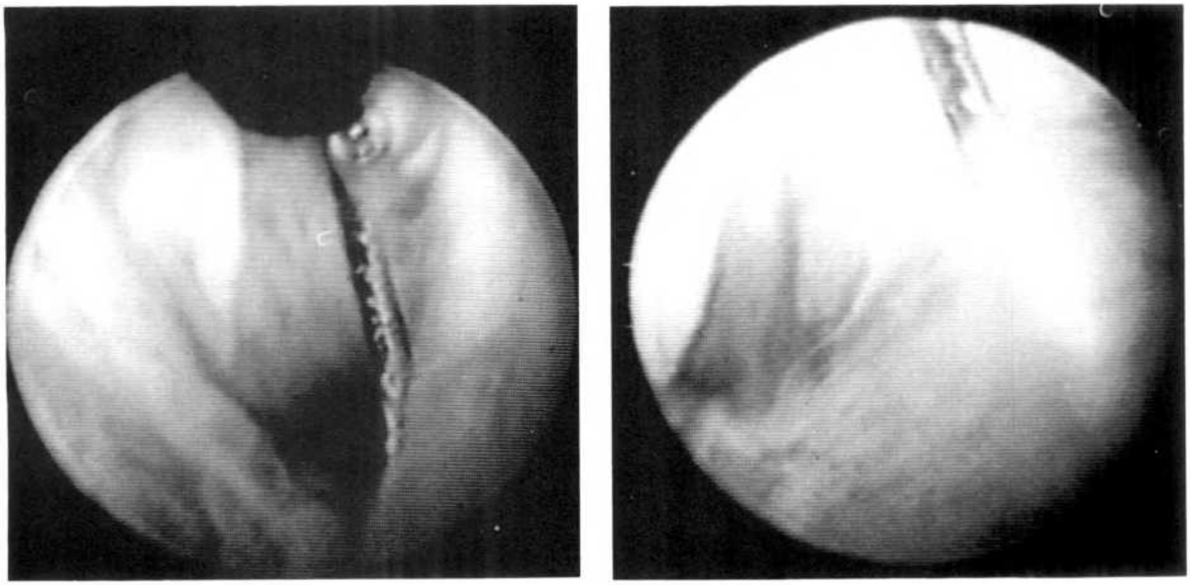

**Fig.** A hook electrode is used to incise the valves at 4 and 8 o'clock. Care must be taken to draw the valve away from the wall of the urethra to avoid injury to the urethral mucosa.

During follow-up the upper tract was monitored and bladder function assessed; before 1980, urodynamic studies were not performed routinely and are therefore not included in this study. Voiding cystourethrograms were performed in all children after 1 and 3 years. At the time of final evaluation all children were more than 5 years of age and voiding patterns were evaluated.

## Results

Of the boys treated with transurethral electroresection only 3 (6%) were incontinent. One patient underwent ablation of the valves only; in the other 2 boys the bladder neck was incised at the time of valve resection. They complained of diurnal and nocturnal enuresis, but urodynamically they showed insufficiency of the bladder neck, small bladder capacity and detrusor instability.

Treatment with anticholinergics resulted in significant improvement in 2 boys. In all patients urinary flow was non-obstructive and no strictures could be detected on the voiding cystourethrograms.

There were no strictures in the boys treated with transurethral electro-incision and none suffered from urinary incontinence that could be related to the valve incision. In 1 patient a small diverticulum of the posterior urethra was found but there were no clinical sequelae.

## Discussion

Posterior urethral valves may present in many different ways. With prenatal ultrasound studies, many boys come to our attention at a much earlier stage. The condition of the upper tract also varies widely. Severe hydronephrosis, obstruction of the ureter at the vesicoureteric junction (especially during bladder filling), vesicoureteric reflux and renal dysplasia are common findings. Regardless of whether a vesicostomy or a high urinary diversion is performed, eventually the valves have to be incised or resected. Depending on the above criteria, the valves can be dealt with immediately or at a later stage. We prefer to treat them as soon as possible.

Many techniques have been described for the treatment of the valves. Most widely used is transurethral electro-incision under direct vision. Percutaneous antegrade destruction (Datta, 1987) has the advantage that the urethra is not damaged by the resectoscope, but the disadvantage is that the area behind the valves cannot be seen easily and the external sphincter may be damaged (Zaontz and Firlit, 1985). The use of a Fogarty balloon catheter to ablate the valves has also been advocated (Diamond and Ransley, 1987), as has the hook (Deane *et al.*, 1988). The advantage of these procedures is that general anaesthesia is not required. We feel that the best way to treat the valves is by a procedure under direct vision. General anaesthesia in these infants is not usually a problem and in those babies where it is a problem, other therapeutic measures may be more appropriate.

Since urodynamic studies were not performed regularly in all patients, the results of the above studies are not discussed here. However, even though the number of incontinent patients is very small, this does not mean that all of these patients have normal bladders; in a number of them, compliance is limited and instability is a common finding (Bauer *et al.*, 1979; Campaiola *et al.*, 1985). Most patients, however, seem to adapt to this situation. Moreover, bladder instability is not believed to be a complication of the valve incision itself. Many boys with valves have a thick walled bladder before they present for treatment and after valve ablation this may change over a period of time.

Prevention of urethral strictures after transurethral electroresection or incision of posterior urethral valves can be accomplished easily. Incision of the bladder neck at the time of valve incision should be avoided (Churchill *et al.*, 1983). In many boys the bladder neck may show signs of primary bladder neck obstruction, but this is rarely the case. Usually the bladder neck is wide on the VCUG and a narrowing merely depicts the thickness of the bladder wall. It should be emphasised that any instrument that is used for valve incision should pass through the urethra into the bladder without encountering any resistance and dilatation of the urethra before the patient undergoes surgery can avoid many problems. A perineal urethrostomy is not necessary and increases the risk of urethral stricture formation. All instruments and catheters should be small (8–10 F) and the transurethral catheter should be removed as soon as possible.

The incidence of complications after transurethral valve incision or resection is reported to be as high as 25% (Myers and Walker, 1981). Our results show a complication rate of 5%. A strict regimen is probably the best way of ensuring a minimal number of complications. Since many boys with posterior urethral valves have other serious problems, a low complication rate following valve resection is of great importance to them.

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# Case Reports

## Fracture of the Corpora Cavernosa and Urethral Rupture during Sexual Intercourse

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### Case Report

A 25-year-old man felt "something go pop" at the moment of penetration, followed by immediate detumescence. Upon withdrawal, the penis became rapidly swollen and had developed the full "aubergine" sign. He had not passed urine prior to admission and had pain when he attempted to do so.

Urethroscopy under general anaesthesia revealed a complete rupture of the urethra in the mid-shaft at the area of maximal bruising. A 14 F Silastic catheter was introduced through the Storz catheter guide once the urethroscope was removed. The injury was explored through a peno-scrotal incision and a complete rupture of the urethra, together with a tear of both corpora cavernosa, were repaired with 3/0 and 2/0 Dexon respectively. He was given cefadroxil for 5 days and the catheter was removed after 6 weeks. Complete abstinence for 6 weeks was advised. On follow-up, his flow rate was 25 ml/s and his erections took 10 weeks to return to normal.

### Comment

Injury to the corpora cavernosa during intercourse is uncommon and associated rupture of the urethra is rare. A little over 100 cases of penile fracture have been reported and a third of these had injury to the urethra (Meares, 1971; Godec *et al.*, 1988). The treatment of choice is immediate surgical repair and the prognosis is good.

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## A Rare Case of Urachal Calculus

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The majority of urachal remnants have a draining connection to the umbilicus and are therefore detected early in life (Crawford *et al.*, 1989). We present a case of urachal calculus under different anatomical conditions.

### Case Report

W.W., a 74-year-old male patient, presented with intractable urinary tract infections caused by *Pseudomonas aeruginosa*. Infravesical obstruction, vesicoureteric reflux or tuberculosis had been excluded. On X-ray a stone was thought to be situated in the bladder (Fig.). Cystoscopy, however, showed only chronic, partly fibrinous cystitis. Despite multiple radiographic and endoscopic investigations the situation could only be clarified during operation. A cherry-sized urachal cyst communicating with the bladder only and filled with a calculus seemed to be the origin of the infection. In April 1980 the urachal remnant was extirpated. Histological examination showed no evidence of malignancy. The stone was composed of calcium phosphate.

It seems remarkable that now, 11 years after surgical treatment, bacteriuria is still present despite specific treatment, adequate urinary volume and no residual

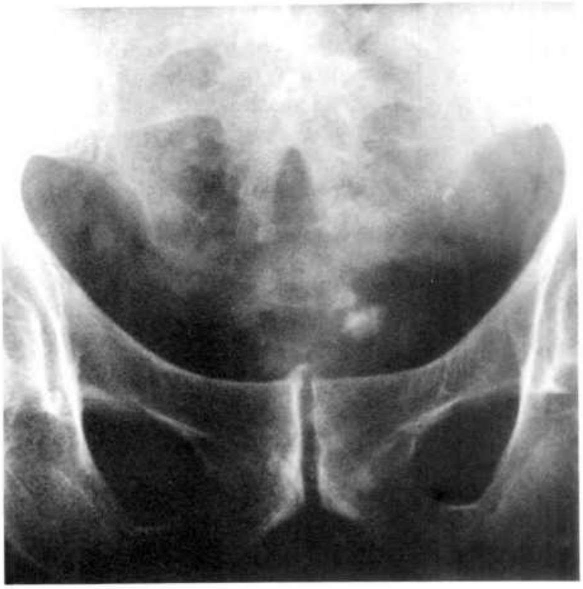

**Fig.** Plain X-ray showing the calculus in close proximity to the bladder.

urine. The patient, however, is free of symptoms and renal function is normal. A recent biopsy showed persisting local non-specific inflammation around the former urachal orifice in the bladder. In contrast to the previously diffuse cystitis, this is now limited to a restricted area of the dome of the bladder.

### Comment

If a calculus in or around the bladder is suspected but cannot be found by cystoscopy, the possibility of a urachal stone should be considered. The resulting problem is chronic urinary tract infection which can persist even after extirpation of the urachal remnant. This patient's history supports the presumption that the bladder mucosa of the surrounding area is not, immunologically, fully differentiated. Surgical treatment, however, has rendered our patient free of symptoms.

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## Physical Examination for Varicocele

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### Case Report

A total of 138 men attending the infertility clinic were examined for the presence of a varicocele. Each man was examined by 2 different doctors in separate clinic rooms. The results were recorded and later compared (Table).

**Table** Correlation of Findings on Clinical Examination by 2 Different Doctors

| | | *First doctor's findings* | | |
|---|---|---|---|---|
| | | *Large varicocele* | *Small varicocele* | *No varicocele* |
| Second doctor's findings | Large varicocele | 10 | 4 | |
| | Small varicocele | 1 | 4 | 7 |
| | No varicocele | 3 | 21 | 88 |

### Comment

There was disagreement between the 2 clinicians in 36/138 patients (26%). There is currently considerable controversy about the merits of varicocele ligation as treatment for male subfertility and lack of objectivity in the clinical examination probably contributes to this controversy. It is important to try to use more objective methods of diagnosis in clinical trials on the efficacy of varicocele ligation.

Requests for reprints to: T. B. Hargreave, University Department of Surgery/Urology, Western General Hospital, Edinburgh EH4 2XU.

## Fatal Tuberculous Meningitis Complicating Tuberculous Epididymitis

C. J. M. BEACOCK, T. H. LYNCH and M. A. HUGHES, *Department of Urology, Queen Elizabeth Hospital, Birmingham*

### Case Report

A 59-year-old man presented to the out-patient clinic with a 1-month history of swelling in the right side of his scrotum. He was well with no urinary symptoms. Examination revealed a swollen, tender right epididymis and a hard, asymmetrically enlarged prostate. A clinical diagnosis of carcinoma of the prostate and epididymitis was made and the patient commenced treatment with trimethoprim 200 mg *bd*. Admission for further investigation, including prostatic biopsy, was planned. A midstream specimen of urine was sterile, containing a few red and white cells.

Eighteen days later the patient was admitted under the care of a physician with a 2-week history of headaches followed by 4 days of vomiting and altered personality state. He had stopped taking his antibiotics after 4 days. He was pyrexial, but without meningism or focal neurological abnormality. The epididymal swelling remained unaltered. CT scan showed no evidence of intracranial haemorrhage or space-occupying lesion.

His cerebrospinal fluid both on admission and 3 days later contained polymorphs but neither acid-fast bacilli nor other organisms were seen. Ampicillin 1 g *qds* was commenced and a diagnosis of malignant meningitis secondary to carcinoma of the prostate was entertained. A prostatic biopsy was taken.

One week after admission his condition deteriorated. Antibiotic therapy was widened to include antituberculous therapy. Epididymal aspirate then contained tubercle bacilli and the prostatic biopsy showed granulomatous prostatitis. The patient rapidly deteriorated and, after a cardiorespiratory arrest and a period of ventilation, he died. Autopsy confirmed tuberculous meningitis.

## Comment

Male genital tuberculosis, particularly epididymitis, constitutes a significant proportion of all TB cases (Gorse and Belshe, 1985). However, progression to fatal tuberculous meningitis has become rare since the introduction of effective chemotherapy. In this case the diagnosis of tuberculosis was delayed until the onset of central nervous system symptoms which prompted re-evaluation of the epididymal swelling and prostate. Even in retrospect the initial diagnosis seems reasonable. Immediate biopsy of the prostate at presentation would have been diagnostic and probably avoided the fatal outcome. However, this action could also have precipitated haematogenous spread of the infection.

Systemic illness is often absent in isolated tuberculosis of the external genitalia and the urine is abnormal in only 30% of cases (Alvarez and McCabe, 1984). It is also unusual for renal TB to be absent in the presence of lower urinary tract tuberculosis.

A high index of suspicion is essential to achieve early diagnosis, the importance of which is illustrated by this case report.

## References

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**Gorse, G. J. and Belshe, F. M.** (1985). Male genital tuberculosis: a review of the literature with instructive case reports. *Rev. Infect. Dis.*, **7**, 511–525.

Requests for reprints to: C. J. M. Beacock, Department of Urology, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH.

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# Traumatic Adrenal Rupture Simulating Renal Injury

D. F. RANDONE, G. F. MOSELE and S. ROCCA ROSSETTI,
*Department of Urology, University of Turin, Turin, Italy*

We report a case of direct traumatic rupture of the adrenal gland.

## Case Report

A 48-year-old man with essential hypertension was struck by an iron bar during his work. On admission the first ultrasound (US) examination of his abdomen was negative, there was no haematuria and his general condition was good. A few hours later, however, a fall in blood pressure and haemoglobin, together with increased pain, led to a second US study which revealed a retroperitoneal haematoma with a possible lesion in the lower pole of the left kidney. An IVU was performed and showed non-function of the left kidney (Fig. 1). Renal arteriography revealed the integrity of the renal pedicle and parenchyma. CT scan confirmed the diagnosis of a large retroperitoneal haematoma (Fig. 2) without obvious vascular or renal lesions. Because of progressive anaemia a thoraco-phrenolaparotomy was performed and the retroperitoneal haematoma was evacuated. The kidney and its pedicle were intact but the superior pole was surrounded by a tense haematoma containing a ruptured and partially necrosed adrenal gland. A left adrenalectomy was performed.

## Comment

The adrenal lesion was isolated and directly caused by the lumbar trauma. Other reported cases refer

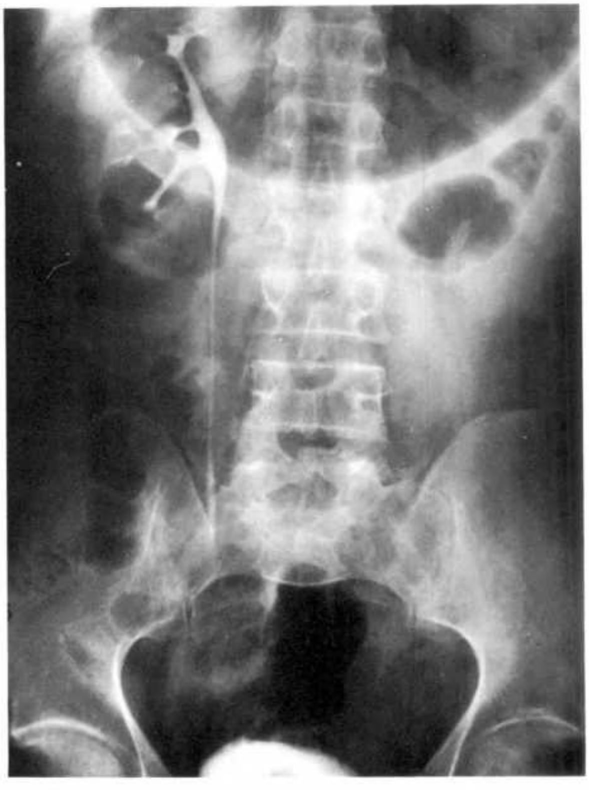

**Fig. 1** Non-function of the left kidney.

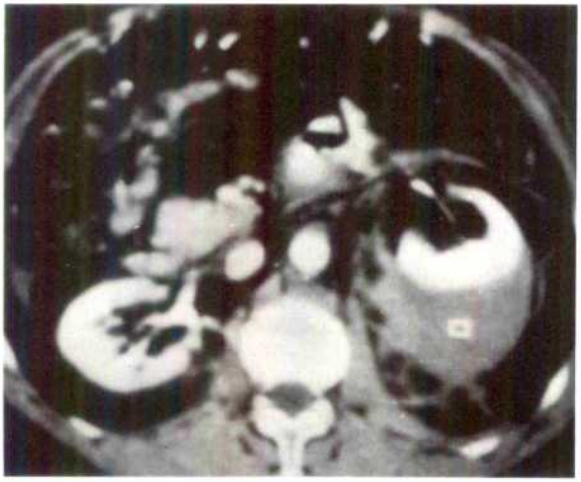

**Fig. 2** Large haematoma located behind the undamaged left kidney.

to patients with associated lesions or indirect trauma (Sevitt, 1955; Karli *et al.*, 1978). Hypertension is frequently associated with adrenal haemorrhage but no evidence of pre-existing adrenal pathology was found in this case. Adrenal traumatic lesions, although frequently resolving spontaneously, can cause serious retroperitoneal haematoma and non-function of the kidney.

## References

**Karli, V. P., Steele, A. and Davis, P.** (1978). Adrenal hemorrhage in the adult. *Medicine*, **57**, 211–221.

**Sevitt, S.** (1955). Post-traumatic adrenal apoplexy. *J. Clin. Pathol.*, **8**, 185–194.

Requests for reprints to: S. Rocca Rossetti, Department of Urology, University of Turin, Corso Polonia 14, 10126 Turin, Italy.

# Massive Scrotal Cystocele with Bladder Cancer

S. H. PAPADIMITRIOU, M. A. CHLEPAS, C. P. KOKINACOS and C. B. PAPADOPOULOS, *Department of Urology, Euagelistria Hospital, Tripolis, Greece*

## Case Report

An 88-year-old man complained of haematuria, dysuria and a long history of left inguinal hernia. Physical examination revealed an obese man with a large left inguinoscrotal mass. The phallus was not visible. On rectal examination the prostate was not palpable. Laboratory studies, including full blood count, blood chemistry studies, urine analysis and urine culture were normal. An intravenous urogram showed good renal function; the distal ureteric segments appeared to extend into the inguinal hernia sac. Cystography demonstrated the entire bladder descending into the scrotum with filling defects (Fig. 1). Urinary cytology revealed a G3 transitional cell carcinoma. CT scan of the scrotum showed an infiltrating bladder tumour (Fig. 2).

## Comment

The urinary bladder is frequently a component of inguinal hernias and has been reported to occur in 10% of all inguinal hernias in men over the age of 50 years; usually, however, only a small portion of the bladder is involved. Bladder hernias extending into the scrotum are extremely rare. Only a few cases of massive bladder herniation combined with bladder cancer have been reported (Croushore and Black, 1979; Bell and Witherington, 1980). Retrograde cystography delineates the bladder protrusion

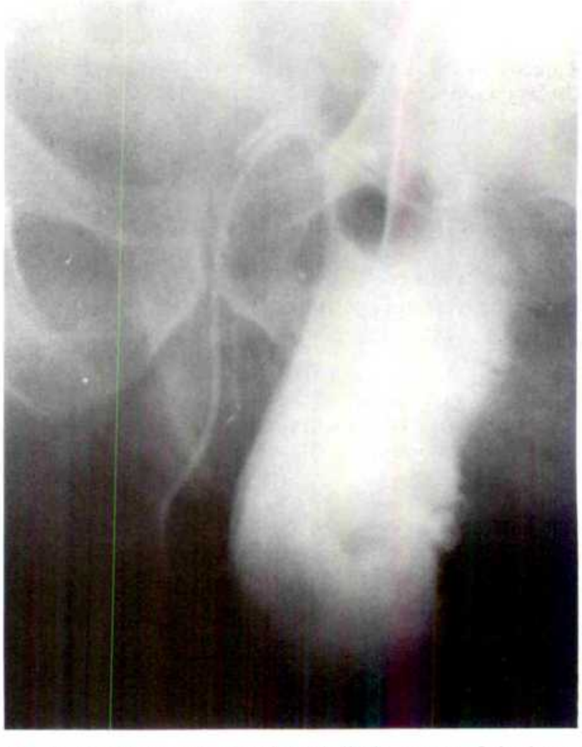

**Fig. 1** Cystogram showing lateral displacement of the lower third of both ureters, the entire bladder descending into a large left inguinal hernia and filling defects in the bladder.

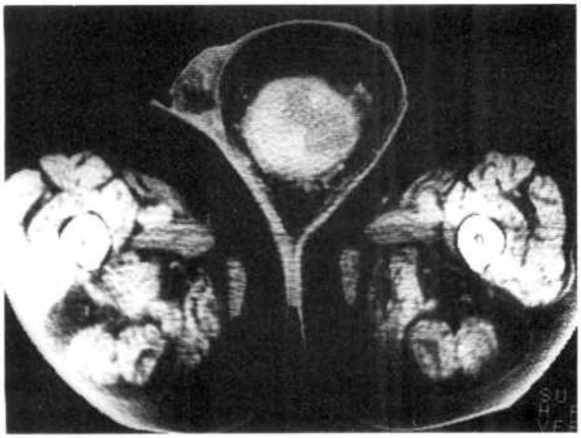

**Fig. 2** CT scan cut transversely through the scrotum showing an infiltrating bladder tumour.

accurately and has been recommended as a routine investigation in men over 50 years of age with inguinal hernia.

## References

**Bell, E. D. and Witherington, R.** (1980). Bladder hernias. *Urology*, **15**, 127–130.

**Croushore, J. H. and Black, R. B.** (1979). Scrotal cystocele. *J. Urol.*, **121**, 541–542.

Requests for reprints to: S. H. Papadimitriou, Department of Urology, Euagelistria Hospital, Tripolis, Greece.

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# Horseshoe Kidney Associated with Left Inferior Vena Cava

I. BILLIET, J. MATTELAER, V. HERPELS and H. VERRESEN,
*Departments of Urology, Radiology, Anatomy and Embryology, Sint-Maarten Hospital and the Catholic University of Leuven, Kortrijk, Belgium*

We report a second case of the rare association between a horseshoe kidney and an infrarenal left caval vein.

## Case Report

A 28-year-old patient was investigated for chronic right flank and abdominal discomfort, present for many years. Colicky pain was present in the peri-umbilical region, transfixing the abdomen anteroposteriorly. There was no fever, weight loss, icterus or urinary abnormalities. Biochemical analysis was normal (ESR, Hb, WCB, liver function tests, renal function tests). Karyotype was 46, X.Y. Abdominal sonography revealed an abnormal structure localised in the mesogastrium, suggesting an ectopic or horseshoe kidney. Further radiological exploration (CT scan, IVU, cavography) confirmed the diagnosis of a horseshoe kidney with a right hydronephrosis on a pelvic junction stenosis. The infrarenal caval vein was situated to the left of the abdominal aorta and crossed under the aorta to the right above the renal veins (Fig.). The parenchymal isthmus was divided and the pelvic junction stenosis was corrected with an Anderson-Hynes pyeloplasty.

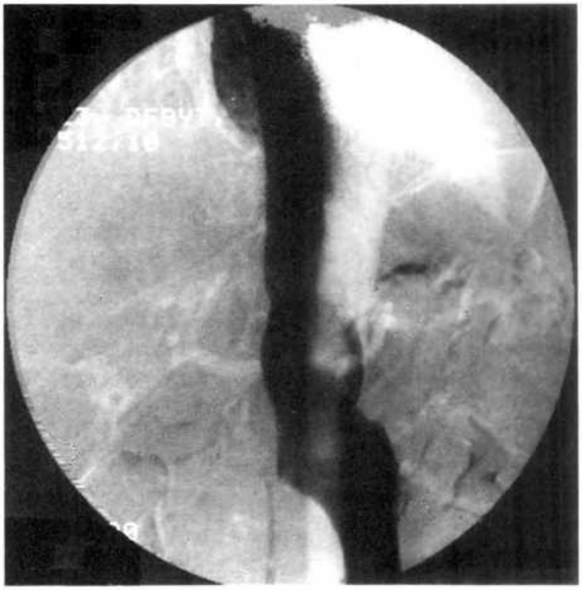

**Fig.** Digital substraction cavography. The left-sided infrarenal vena cava crosses to the right above the level of the renal veins and behind the aorta, ending in a normally positioned right atrium.

## Comment

Horseshoe kidneys occur in 0.25% of the population. In nearly one-third of these patients other congenital abnormalities are present that involve the urogenital, skeletal, central nervous or cardiovascular systems. An increased incidence of horseshoe kidney is found in trisomy 18 and Turner's syndrome (Perlmutter *et al.*, 1987). The associated anomaly of a left infrarenal vena cava has been reported only once (Boyden, 1931).

The development of a horseshoe kidney and formation of the inferior vena cava both occur in the seventh week of gestation and can be the result of the same disturbance in embryogenesis. The origin of the left inferior vena cava in our patient was probably the persistence of the left vena sacrocardinalis (Boyden, 1931; Grünwald, 1938), while in normal development the right vena sacrocardinalis forms the infrarenal vena cava.

## References

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**Grünwald, P.** (1938). Die Entwicklung der Vena Cava Caudalis. *Z. Mikrosk. Anat. Forsch.*, **43**, 275.

**Perlmutter, A. D., Retik, A. B. and Bauer, S. B.** (1987). Anomalies of the upper urinary tract. In *Campbell's Urology*, ed. Walsh, P. C., Ruben, F. G., Perlmutter, A. D. and Stamey, T. A. Fifth edition. Pp. 1686–1692. Philadelphia: Saunders.

Requests for reprints to: I. Billiet, Department of Urology, Ziekenhuis Sint-Maarten, Burg. Vercruysselaan 5, B-8500 Kortrijk, Belgium.

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# Cavernous Haemangioma of the Glans Penis

S. KHANNA, *Department of Urology, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

Penile haemangiomas are extremely rare and few have been reported (Lane, 1953; Senoh *et al.*, 1981). The aetiology is unknown, although it is usually thought to be congenital or due to vascular neoplasia; some have reported its development following trauma (Senoh *et al.*, 1986). One such case of cavernous haemangioma of the glans penis is reported.

## Case Report

A 30-year-old male presented with bleeding from the glans penis following coitus on 2 occasions over the preceding year.

On examination there was an elevated, circular lesion on the dorsal portion of the glans penis about the size of a pea (Fig.). It was bluish purple, compressible and non-tender, with a raspberry-like appearance. No similar lesion was seen elsewhere on the body and there was no relevant family history.

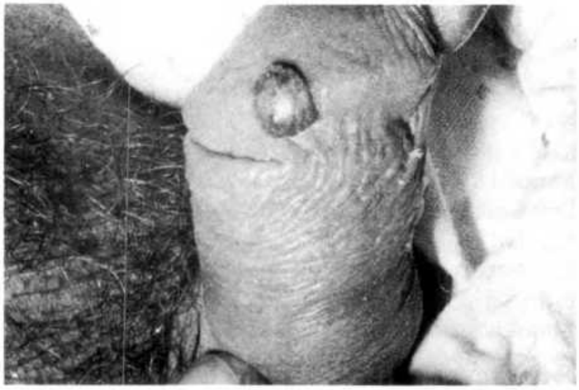

**Fig.** Well circumscribed elevated angiomatous lesion of glans.

The lesion was excised and on histological examination it was reported as having thin walled, irregularly dilated, anastomosing vessels lined by endothelial cells. No encapsulation by the fibrous tissue was noted.

## Acknowledgement

I am grateful to Dr B. D. Radotra, Department of Morbid Anatomy, for providing the histopathological report on this patient.

## References

**Lane, J. W.** (1953). Haemangioma of the glans penis. *United States Armed Forces Medical Journal*, **4**, 139–140.

**Senoh, H., Ichikawa, Y., Okuyama, A.** ***et al.*** (1986). Cavernous haemangioma of scrotum and penile shaft. *Urol. Int.*, **41**, 309–311.

**Senoh, K., Miyazaki, T., Kikuchi, I.** ***et al.*** (1981). Angiomatous lesions of the glans penis. *Urology*, **27**, 194–196.

Requests for reprints to: S. Khanna, Department of Urology, Sir Ganga Ram Hospital, Old Rajinder Nagar, New Delhi-110060, India.

*British Journal of Urology* (1991), **67**, 333

# Correspondence

Dear Sir,

*re* **Assessment of residual urine in men following catheterisation.** S. F. Purkiss. *Br. J. Urol.*, **66**, 279–280, 1990.

Mr Purkiss indicated in the first paragraph of his article that transvaginal ultrasound (B. T. Haylen *et al. Br. J. Urol.*, **64**, 353–356, 1989) could only assess bladder volumes after the catheter had been removed. Transvaginal ultrasound and the equivalent technique in men, transrectal ultrasound (B. T. Haylen *et al. J. Urol.*, **143**, 687–689, 1990) can measure bladder volumes, post-catheterisation or otherwise, with or without the catheter *in situ*. Should the balloon of a Foley catheter (if this is the catheter used) be inflated at the time of measurement, then the known volume in the balloon would simply be deducted from the calculation for the total volume to obtain the true volume.

We agree with the thrust of Mr Purkiss's article, in that Foley catheters in particular are relatively ineffective in completely draining bladders in both sexes. We found this to be the situation using size 14F catheters and it is interesting that Mr Purkiss has found little improvement using a 16F catheter.

The accuracy of the dilutional method used in this article has not been tested. Like other dilutional techniques used to measure bladder volumes (F. Hinman and C. E. Cox. *J. Urol.*, **97**, 641–645, 1967) involving multiple steps and subsequent laboratory analysis, there are clear practical shortcomings and the potential for inaccuracies. Transvaginal and transrectal ultrasound, however, allow immediate, direct and reliable visualisation of bladder volumes as well as their accurate measurement.

Yours faithfully,

B. T. Haylen
Obstetrics and Gynaecology, Urogynaecology and Urodynamics, William Bland Centre, Macquarie Street, Sydney, Australia.

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Dear Sir,

*re* **Disappearing staghorns.** M. D. Griffith-Jones. *Br. J. Urol.*, **66**, 327, 1990.

This Case Report was of interest but is misleading by suggesting that long-term, low-dose trimethoprim resulting in a decrease in calculus size has not been reported previously.

*In vitro* and *in vivo* studies have shown that struvite calculi may partially dissolve in the presence of sterile urine (T. A. Stamey, 1972). Infection Stones in Urinary Infections. P. 213. Baltimore: Williams and Wilkins; D. P. Griffith *et al. J. Urol.*, **121**, 711–715, 1979). Long-term culture-specific antimicrobials may reduce the magnitude of urinary infection even if sterility does not result. A reduction of the colony count from $10^7$ to $10^5$/ml reduces the urease production by 99% (D. P. Griffith and C. A. Osborne. *Miner. Electrolyte Metab.*, **13**, 278–285, 1987). In 1979 Griffith *et al.* maintained sterile urine in 9 patients with struvite calculi using a variety of culture-specific antibiotics including trimethoprim. Five of these patients had significant stone dissolution. As trimethoprim did not maintain this reported patient's urine sterility, it is more likely that the intermittent culture-specific antibiotics administered resulted in partial stone dissolution. In view of the fact that 90% of *Proteus* infections are sensitive to ampicillin or penicillin (R. M. Feit and W. R. Fair. *J. Urol.*, **122**, 592–594, 1979), I suggest that long-term ampicillin or penicillin is more appropriate suppressive therapy than trimethoprim if facilities to provide culture-specific antibiotics are not available to patients with residual struvite calculi.

Yours faithfully,

M. Gleeson
Department of Urology, Meath Hospital, Dublin.

British Journal of Urology (1991), 67, 334

# Notices

## British Association of Urological Surgeons

**President:** R. E. Williams, MD, ChM, FRCS, FRCSE

*Annual Meeting: Glasgow. 25–28 June 1991*

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

## Shackman Travelling Fellowship 1992

Applications are invited from Medical Practitioners registered in the United Kingdom who are either trainees in Urology or Organ Transplantation or Consultant Urological Surgeons or Consultant Surgeons with a major commitment to transplantation of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1991.

Further particulars and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

## Dantec Urology Prize

An annual prize is awarded by Dantec for the best scientific paper contributing towards the understanding of the function of the urinary tract, which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will be known as The Dantec Award for Contribution to the Understanding of Urinary Tract Function. The prize will consist of a £400 travel voucher together with a token presentation gift. The prize will be presented at the BAUS Annual Meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered. Three members of BAUS Council will be nominated at the February meeting of Council to act as adjudicators. All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to the Honorary Secretary of the British Association of Urological Surgeons. The winner of the prize will be announced at the Annual Meeting, when the official presentation will be made.

## Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000 to support a clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. Entries will be judged by three members of Council nominated at the February meeting and the winner will be announced at the Annual General Meeting.

*British Journal of Urology* (1991), **67**, 335–336

# Diary

1991

| | |
|---|---|
| March 8–9 | Urology for the FRCS. Contact: Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London, WC2H 8JE. Tel: 071 240 9115. |
| March 11–15 | Uro-Andrology Course including Male Infertility and the Management of Impotence. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| March 16–17 | International Symposium of Operative Andrology. For further details of this course and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| April 4–6 | Senior Registrars' Meeting (SURG), Cambridge. Contact: Mr I Eardley, Dept of Urology, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ. Tel: 0223 245151. |
| April 4–5 | Annual Meeting and Teaching Course—Urological Computing Society. Contact: Lindsay Morrison, Membership Secretary, Urological Computing Society, Southern General Hospital, Glasgow, G51 4TF. |
| April 8–28 | Short Courses in Urology and Nephrology including: The Management of Benign and Malignant Prostatic Disease, Paediatric Urology, The Management of Urological Cancers, Tropical Diseases and GU Medicine, Reconstructive Surgery. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| April 24–28 | 1991 Duke Urologic Assembly. St Thomas, US Virgin Islands. Contact: Linda Mace, Assembly Coordinator, Box 3707, Duke Medical Center, Durham, NC 27710, USA. |
| April 26 | Bradford Urology Symposium. Bradford Royal Infirmary. Contact: Mr G. M. Flannigan, Bradford Royal Infirmary, Bradford BD9 6RJ. |
| April 12–13 | Second Meeting of European Society of Paediatric Urology, Beaune, France. "Neurogenic Bladder in Children and Adolescents". Contact: Dr P. Mouriquand, "Le Dizenier", 11 Impasse Mouillard, 69009 Lyon, France. |
| April 14–19 | Forty-fourth Annual Scientific Meeting of the Urological Society of Australasia, Sheraton Mirage Hotel, Gold Coast, Queensland, Australia. Contact: G. Holmes, President, Brisbane Urology Clinic, 11th Floor, 149 Wickham Terrace, Brisbane, QLD 4000. |
| May 3–4 | Third International Meeting of Andrology<br>Non-surgical Treatment of Impotence. Rome, Italy. Contact: Dr R. Vanzetti, MEDICON ITALIA srl, Piazza Mancini, 4, 00196 Rome, Italy. |
| May 30–31 | Surgical Andrology, St Bartholomew's Hospital, London. Contact: BAUS Office. |

| | |
|---|---|
| May 25–26 | Fifty-sixth Congress of the Societe Belge d'Urologie, Brussels, Belgium. Contact: F. F. Wart, C.H.U.–I.M.C.A.G., Division of Urology, Bd Zoe Drion, 1, B.6.000 Charleroi–Belgium. |
| June 2–6 | American Urological Association, Metro Toronto Convention Centre, Toronto, Canada. |
| June 7–8 | Fourth Pediatric Surgery Research Workshop, Berlin, Germany. Contact: Dr F. Schier, Pediatric Surgery, Univ.-Klinikum Steglitz, Hindernburgdamm 30, 1000 Berlin 45, Germany. Tel: (0 30) 7 98 41 81/29 09. |
| June 12–15 | Congress of the Portuguese Association of Urology. Funchal, Madeira Island. Contact: Dr Manuel Mendes Silva, Rua Consiglieri Pedrosa, 123, 2745 Queluz, Portugal. Tel: (351-1) 4354044/9. |
| June 16–20 | Canadian Urological Association Annual Meeting, Ottowa. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6. |
| June 17–22 | Diploma Course Revision Block. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| June 18–22 | Tenth World Congress for Sexology, Amsterdam, The Netherlands. Contact: Congress Secretariat, 10th World Congress for Sexology, c/o RAI Organisatie Bureau Amsterdam bv, Europaplein 12, 1078 GZ Amsterdam, The Netherlands. |
| June 25–28 | BAUS Annual Meeting, Scottish Exhibition and Conference Centre, Glasgow. Contact: BAUS office. |
| July 2–3 | Diploma Course Examination. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| August 21–23 | Edinburgh Urological Festival. Contact: Urological Festival Secretary, Department of Surgery/Urology, Western General Hospital, Crewe Rd, Edinburgh EH4 2XU. |
| August 25–31 | First Urology Summer Forum, Oosterbeek. Contact: Secretariat Organization, PO Box 226, 3830 AE LEUSDEN, The Netherlands. |
| September 1–6 | 6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96. |
| September 4–7 | Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllői ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016. |
| September 16–19 | Second Beijing International Symposium on Recent Advances in Urology, Beijing, China. Contact: Gu Fang-liu, Institute of Urology, Beijing Medical University, 1 Da Hong Luo Chang, West District, Beijing 100034, China. |

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REVIEW

# The Encrustation of Indwelling Catheters

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Long-term urethral catheterisation is frequently necessary for patients with intractable urinary incontinence or urinary retention. This procedure is employed in as many as 16 to 28% of patients in chronic care facilities (Cools and Van Der Meer, 1986; Kunin *et al.*, 1987) and in 4% of patients nursed at home (unpublished data). More than 50% of these patients may suffer problems associated with encrustation and blockage of their catheter (Cools and Van Der Meer, 1986). Blockage can cause incontinence due to urinary bypassing of the catheter, or acute pain and discomfort associated with urinary retention. These problems are particularly distressing to patients being cared for in the community, where professional help is not immediately available. In addition, the coarse, irregular surface of the deposits may result in pain and physical trauma to the urethra when the catheter is removed, increasing the risk of infection. Catheter encrustation therefore has serious implications not only for patient management and comfort, but also for maximising efficiency and effectiveness of health care provision.

Other complications of catheterisation may be inter-related with encrustation. Inflammatory responses or toxic reactions to components leached from the catheter material may be exacerbated by the irritant effect of encrustations on bladder or urethral mucosa. Conversely, increased production of cellular debris and exudate from such reactions may contribute to potential blockage initiated by the encrustations.

Despite modern closed drainage systems, over 90% of patients undergoing long-term catheterisation will develop bacteriuria within 4 weeks (Slade and Gillespie, 1985). A different distribution of micro-organisms, and in particular a higher proportion of Gram-negative bacilli, is reported in the urine from catheterised compared with non-catheterised patients (Cools and Van Der Meer, 1986). Complex mixed communities of micro-organisms, frequently unresponsive to antibiotic therapy (MacFarlane, 1985) or antiseptic bladder washouts (Stickler *et al.*, 1987), develop during longer periods of catheterisation. Encrustation may protect bacteria from therapeutic agents and thus lead to the persistence of infection.

## Encrustation

### *Location of encrustations*

Encrustations form only on the surfaces of catheters and balloons which are exposed to urine and are not found on surfaces in close contact with the bladder or urethral mucosa. The mucinous layer overlying the bladder mucosa may be a defence mechanism preventing adhesion of deposits (Kunin, 1987). This surface layer prevents bacterial adherence and invasion of the bladder wall and its anti-adherence activity can be removed by treatment with dilute acid (Parsons *et al.*, 1979). This has considerable implications regarding the use of certain bladder washout preparations which contain dilute acids.

### *Composition of encrustations*

Examination of encrusted material by X-ray diffraction and by chemical analysis has identified ammonium magnesium phosphate (struvite) and calcium phosphate as major components (Hedelin *et al.*, 1985; Cox *et al.*, 1987). However, calcium oxalate may be an important component in a small number of patients (Hedelin *et al.*, 1984).

A significant positive correlation exists between the frequency of catheter blockage and the proportion of the encrusting material present as calcium

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phosphate (Hedelin *et al.*, 1985). X-ray analysis has shown that catheter deposits contain fully crystalline struvite, but that calcium phosphate is present as poorly crystalline hydroxyapatite (Cox *et al.*, 1987). This "powdery" form of calcium phosphate may occlude the catheter lumen more easily than larger crystals, thus explaining the observations of Hedelin *et al.* (1985).

With the exception of protein, the organic components of encrustations have not been characterised. However, large amounts of mucus are voided by patients with long-term indwelling catheters (Kunin, 1987) and an increase in urinary mucoproteins and mucopolysaccharides has been associated with infection by some Gram-negative bacteria (Griffith, 1978). During conditions of low urine flow or high osmolality, this mucus may become inspissated and contribute to catheter blockage.

### *The role of urease-producing micro-organisms*

Infection with urease-producing micro-organisms produces an alkaline urine which provides ideal conditions for the precipitation of struvite. Struvite stones in the upper urinary tract have long been termed "infection stones" due to their association with urease-producing micro-organisms. An analogy between "infection stone" development and the formation of catheter encrustations has been proposed (Norberg *et al.*, 1980; Kunin, 1987). *Proteus mirabilis* is most commonly associated with stone formation and has been significantly associated with obstructed catheters (Kunin, 1989). In animal models, however, virtually all urease-producing organisms, including *Ureaplasma urealyticum*, are calculogenic (Rosenstein *et al.*, 1980).

Catheters have been encrusted *in vitro* using artificial urine supplemented with urease (Cox *et al.*, 1989). Calcium phosphate is precipitated initially followed by struvite as the pH rises above 7.2.

Scanning electron micrographs of encrusted catheters have revealed the presence of micro-organisms underlying mineral deposits (Cox *et al.*, 1989). Furthermore, the pH of the urine within a blocked catheter is higher than that of urine flowing from a newly inserted catheter (Norberg *et al.*, 1980). This suggests a localised production of urease by micro-organisms colonising the catheter surface.

Whilst the presence of urease appears to play a critical role in crystallisation leading to catheter obstruction, urease-producing organisms are not always detected in the urine of patients with blocked catheters (Hedelin *et al.*, 1985). This anomaly may be explained by variation in sampling methods or by the protective mechanisms of either an organic biofilm or encrusting material. Alternatively, urease production might be due to organisms such as *Ureaplasma urealyticum*, which are not detected by conventional culture methods.

Some studies have recovered urease-producing organisms with similar frequency in urine from blocked and unblocked catheters (Kunin *et al.*, 1987). These observations suggest that other factors may contribute to, or inhibit, crystallisation in some patients.

### *Patient characteristics*

Susceptibility to catheter encrustation may be a "patient-related" phenomenon and 2 main groups of patients, "blockers" and "non-blockers", have been identified by Kunin *et al.* (1987). "Blockers" are "those who consistently and repeatedly develop extensive encrustations on their urinary catheter within a few days to several weeks". These patients excrete a more alkaline urine than "non-blockers"; however, no consistent correlation between urine composition and encrustation composition has been observed (Kunin, 1989). Patient variation may also account for the lack of correlation between the time *in situ* and the extent of catheter encrustation (Hedelin *et al.*, 1985).

In a recent survey of 81 catheterised patients in the community, the observed frequency of catheter blockage was unrelated to age, sex, medical history or mobility (unpublished data).

The presence of urinary inhibitors of crystallisation may account for the observed differential susceptibility to encrustation. Two major inhibitors of crystal formation have been described: low molecular weight materials such as pyrophosphate, citrate and magnesium, and macromolecular material consisting of glycosaminoglycans, uromucoids and polyribonucleotides, etc. The role of both groups in the pathogenesis of calcium stone formation in the upper urinary tract has received considerable attention (Kohri *et al.*, 1989) but their involvement in catheter encrustation is unknown. However, sulphated glycosaminoglycans have been used to inhibit adhesion of cells to non-biological materials (Maroudas and Lindenbaum, 1987).

## Catheter Management

### *Catheter material*

Catheters made from 100% silicone or latex coated with a tightly bonded layer of silicone-elastomer are usually chosen for long-term use since they produce less urethral inflammation than other materials (Nacey *et al.*, 1986). More recently, catheters with a "hydrogel", polymer coating, which readily absorbs aqueous fluids, have been introduced. It has been suggested that the hydrogel catheter surface may resist bacterial colonisation more effectively since adhesion of cells to non-biological materials can be inhibited by dilute solutions of space-filling hydrophilic polymers (Maroudas, 1975).

Encrustation occurs on all types of catheters (Hukins *et al.*, 1983; Cox *et al.*, 1988) and the conflicting reports of differing susceptibility to encrustation shown by different catheter materials probably reflects patient variation rather than the qualities of the materials currently available. The use of more expensive catheters for patients experiencing frequent blockage therefore requires justification on an individual patient basis. There is some evidence to suggest that less encrustation occurs on conformable catheters (Brocklehurst *et al.*, 1988) and this may be due to the dislodgement of deposits by the pulsatile flow of urine through the catheter.

Catheter surface morphology does not affect the sites of crystallisation *in vitro* (Cox, 1990). However, since Gram-negative bacilli adhere differentially to catheter materials (Sugarman, 1982), bacterial colonisation may be influenced by catheter surface properties. The anti-bacterial properties of silver have been used in silver alloy-coated catheters which are associated with a reduced incidence of bacteriuria (Liedberg and Lundeberg, 1990). New developments in catheter coating could be directed towards limiting colonisation by urease-producing micro-organisms.

### *Catheter size*

Large catheters (>20F) have been associated with leakage and blockage in elderly, hospitalised patients (Kennedy *et al.*, 1983). Large catheters and balloons increase bladder irritability, causing spasms and leakage of urine, and may block urethral glands, allowing accumulation of debris with consequent infection and blockage. The use of the smallest size of catheter compatible with free flow of urine, together with a balloon of 5 to 15 ml, is therefore recommended for long-term catheterisation (Kunin, 1987).

### *Use of antibiotics and antiseptics*

There is general agreement that antibiotics will not prevent infection in long-term catheterised patients (Kunin, 1987). Whilst systemic antibiotic therapy may be effective in eradicating one episode of infection, bacteriuria soon recurs and resistant strains may emerge (Dudley and Barriere, 1981). Similarly, although bladder irrigation with antibiotic or antiseptic solutions has been advocated and continues to be used, emergence of resistant strains is again favoured (Dudley and Barriere, 1981). The benefit of the widespread use of chlorhexidine in bladder washouts, lubricating gels and antiseptic cleaning solutions is disputed (Stickler *et al.*, 1987). Chlorhexidine is ineffectual against a number of commonly occurring urinary pathogens, but may be active against some bacteria in the normal urethral flora (Stickler *et al.*, 1987). Removal of these organisms will allow subsequent colonisation by more resistant organisms, which may include urease-producers.

Micro-organisms growing in a surface biofilm are often present in thick layers associated with a matrix of fibrous polysaccharides which protect them from antibiotic or antiseptic treatment (Gristina and Costerton, 1984). Micro-organisms associated with encrustations may also be protected by the deposition of minerals around them. Furthermore, the altered physiological state of biofilm inhabitants may contribute to their resistance (Brown *et al.*, 1988). However, removal of the catheter does not control the problem of encrustation on subsequent catheters, indicating the continued presence of a bacterial focus in the bladder or urethra.

### *Control of urinary osmolality and pH*

A high fluid intake is frequently recommended for catheterised patients (Kunin, 1987). In practice, however, it is difficult to maintain a high diuresis and low urine osmolality over a long period of time by increasing water intake (Hedelin *et al.*, 1985). Furthermore, urinary solute concentration is not correlated with the degree of encrustation (Kunin, 1989), although diuresis may assist in voiding micro-organisms from the bladder.

Prevention of struvite precipitation by maintaining a low urinary pH is difficult, particularly in the presence of urease production. Oral intakes of acidic liquids such as cranberry juice or acidifying agents such as ammonium chloride, ascorbic acid and methenamine hippurate have been recommended (Kunin, 1987), but effectiveness is dependent on large doses which are often unsuitable for long-term care.

### *Current catheter management*

Current management of catheter encrustation is varied but remains largely dependent on the use of bladder washout preparations. Removal of deposits by many washout reagents, including saline, antiseptics, antibiotics and even tap water, is probably influenced more by physical forces than by chemical interactions. However, irrigation of catheters with acidic solutions such as Suby G (a weak solution of citric acid with magnesium oxide) (CliniMed., High Wycombe) has been shown to dissolve encrustations *in vitro* (Hesse *et al.*, 1989) and is now used extensively in practice.

Whilst it may be argued that increasing catheter time *in situ* by use of suitable irrigation fluids reduces tissue irritation and patient distress caused by frequent catheter changes, the risks of adverse effects must be weighed against the potential benefits. Dilute acid solutions can remove the surface layer of mucus in the bladder (Parsons *et al.*, 1979) and increased exfoliation of bladder mucosal cells has been observed to follow washouts (Elliott *et al.*, 1989). An increased risk of infection accompanies frequent breaking of the closed drainage system, and chemical cystitis or mechanical damage to the bladder may facilitate bacterial invasion into deeper submucosal layers of the bladder wall.

Further careful assessment of bladder washout preparations is essential to determine optimum regimes for effectiveness, whilst minimising potentially detrimental effects of long-term use. Accurate evaluation tools are therefore of great importance. Patients retain a consistent overall pattern of susceptibility to catheter encrustation and blockage. However, the actual length of time an individual catheter may remain functional can vary (Norberg *et al.*, 1980). This variability is a potential source of error in the comparison of different methods of care, and Norberg *et al.* (1980) suggest that it is necessary to take the median "lives" of 3 to 5 catheters to obtain a reliable parameter.

Despite the potential problems associated with long-term catheterisation, no practical alternative exists for many chronically ill patients, to whom the catheter is an "aid to daily living". However, recurrent encrustation causes discomfort to patients and is costly both in materials and in increased demands on medical and nursing services. A greater understanding of the factors contributing to catheter encrustation is required to aid the establishment of effective catheter care policies. Such policies can then be used to form the basis for appropriate individualised programmes of care which will improve the "acceptance" of the catheter by patients and enhance their personal independence.

## Acknowledgement

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# Acquired Renal Cystic Disease: Implications for the Urologist

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Summary—Acquired cystic kidney disease has become increasingly recognised as a significant risk in patients with end-stage renal disease, especially in those maintained on chronic haemodialysis and peritoneal dialysis. A review of the literature indicates that nearly 50% of patients on dialysis for more than 3 years develop renal cystic changes. The major complications of this condition are neoplasia and spontaneous renal haemorrhage. The risk of developing renal carcinoma has been estimated to be more than 30 times higher in dialysis patients with cystic changes than in the general population. Our experience with 5 patients is reported, including 3 with renal tumours and 1 with metastatic disease. Careful surveillance of dialysis patients using yearly ultrasonography and computed tomography is recommended. The evolving indications for radical nephrectomy in this disease are discussed.

The development of cystic changes in the kidneys of patients receiving haemodialysis was first described little more than a decade ago (Dunnill *et al.*, 1977). Although these patients were for the most part clinically asymptomatic, it was notable that many of the kidneys harboured renal carcinomas. Since Dunnill's review, there have been several reviews of acquired cystic kidney disease (ACKD) in patients with end-stage renal disease (ESRD) (Brendler *et al.*, 1984; Gardner and Evan, 1984; Gehrig *et al.*, 1985; Ishikawa, 1985; Basile *et al.*, 1988). ACKD is reported to develop in a third or more of patients maintained on haemodialysis, and the likelihood of developing ACKD increases with the length of dialysis. Up to 45% of patients with ACKD may develop renal neoplasms, including renal adenocarcinomas which have metastasised (Fayemi and Ali, 1980; Ishikawa and Shinoda, 1983; Cho *et al.*, 1984). We review our experience in patients with end-stage renal disease who have developed acquired cystic kidney disease and discuss the clinical management of this entity.

## Patients and Methods

Patients with acquired cystic kidney disease treated at the Boston Veterans Affairs and the Boston University Medical Center Hospitals were identified by selecting from the pathology and clinical files cases of renal tumours or cysts in patients with uraemia. These 5 patients, 4 male and 1 female, with ages ranging from 38 to 75 years, were receiving maintenance haemodialysis for a period of 4 to 10 years before clinical presentation or death (Table). In 2 cases, diagnostic material was obtained at nephrectomy (bilateral in 1 case) and 2 patients were examined at autopsy. In 1 case, diagnostic material was obtained at surgery and subsequent autopsy.

## Results

Three of 5 patients had renal neoplasms, 2 of which were suspected on clinical grounds and prompted nephrectomies. In 1 case, neoplasia was noted only after nephrectomy and pathological examination of the kidney. The neoplasms ranged in size from microscopic to 3.5 cm in diameter. In case no. 3 the

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**Table** Summary of Pathological and Clinical Features in 5 Cases of ACKD

| *Case no.* | *Cause of ESRD* | *Duration of dialysis (years)* | *Presenting symptom* | *Neoplasm* | *Invasion/ metastases* |
|---|---|---|---|---|---|
| 1 | CPN | 9 | None | No | — |
| 2 | HTN | 6 | Flank pain | Yes | Yes |
| 3 | CPN | 5 | Bleeding | Yes | No |
| 4 | HTN | 4 | None | No | — |
| 5 | CGN | 10 | Bleeding | Yes | Yes |

ESRD = end-stage renal disease. CPN = chronic pyelonephritis. HTN = hypertensive nephropathy. CGN = chronic glomerulonephritis.

tumours were multiple and small (less than 0.7 cm in diameter). There was extracapsular invasion in case nos 2 and 5, with extension into the perinephric fat in case no. 2, and in case no. 5 the tumour had metastasised to the renal hilar nodes.

## Case Reports

*Case no. 1.* J.S., a 56-year-old white male with end-stage renal disease, presented for pre-transplant evaluation. The diagnosis was chronic pyelonephritis due to bilateral grade II vesicoureteric reflux and he had been maintained on chronic haemodialysis for 9 years. Bilateral simple nephrectomies were performed in anticipation of cadaveric renal transplantation. The right and left kidneys weighed 125 and 150 g respectively and contained numerous cysts with gross distribution and microscopic appearance consistent with ACKD (Fig. 1). No renal neoplasms were noted.

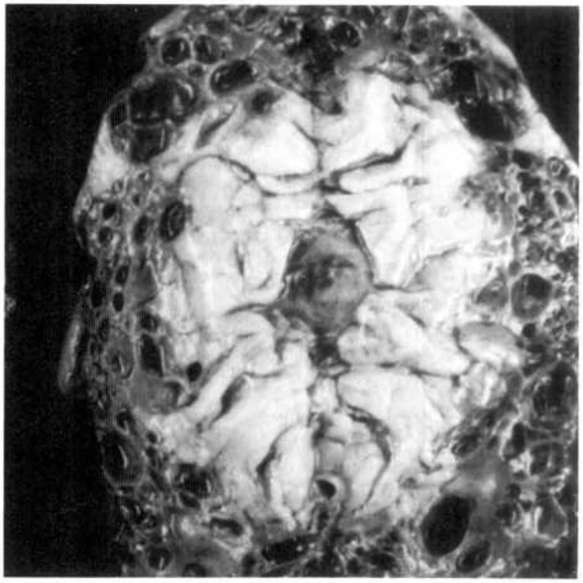

**Fig. 1** Gross pathological appearance of kidney in case no. 1. Small cysts are diffusely distributed throughout the parenchyma.

*Case no. 2.* K.C., a 59-year-old female with hypertensive nephropathy receiving haemodialysis for 6 years, presented with right flank pain. Renal ultrasound and CT scan revealed a large left renal cyst. The cyst aspirate was haemorrhagic and an irregular cyst wall was noted on contrast injection. A left radical nephrectomy was performed. Pathological examination revealed a small kidney containing multiple small cysts. Multiple microscopic adenomas were present, some within cysts. Two larger tumours, confined to the parenchyma, measured 1.7 and 2.0 cm in diameter. The largest tumour measured 3.5 cm and was focally invasive into the perinephric fat. The patient did well until 1 year later, when she was evaluated for signs of biliary obstruction. A mass in the head of the pancreas was noted but the patient refused biopsy. Subsequently, she had repeated hospitalisations for sepsis and presented 1 year later with an infected right hip; 1.5 L of purulent material were drained from a hip abscess from which *Staphylococcus* and *Pseudomonas* species grew on culture. She died from generalised sepsis in June 1987, 23 months after nephrectomy. Although her contralateral kidney appeared involved by ACKD on CT scan, this could not be confirmed as permission for autopsy was refused.

*Case no. 3.* E.R., a 65-year-old white male, was first treated for bilateral pelviureteric obstruction in 1953 by placement of nephrostomy tubes. The patient consistently refused any management other than chronic nephrostomy tube drainage. Recurrent episodes of pyelonephritis ultimately resulted in renal failure and he began maintenance haemodialysis in 1981. In 1987 he presented with bleeding from his right nephrostomy tube. Nephrostography and CT scan showed filling defects in the right renal collecting system and bilateral renal cysts. A right radical nephrectomy was performed. The kidney was small, with multiple renal cysts (Fig. 2). Deposits of oxalate crystals were scattered throughout the parenchyma (Fig. 3). Multiple small renal tumours up to 0.7 cm in diameter without evidence of capsular invasion were seen (Figs 4 and 5). No masses in the remaining kidney have been detected by yearly CT scans.

*Case no. 4.* H.F., a 75-year-old male with chronic renal failure secondary to hypertensive nephrosclerosis, died from complications of hepatitis and bacterial endocarditis. He had received haemodialysis for 4 years prior to death. On autopsy, multiple renal cysts in small end-stage kidneys were encountered. No renal tumours or abscesses were seen.

*Case no. 5.* D.C., a 38-year-old white male with ESRD due to membranoproliferative glomerulonephritis, was maintained on haemodialysis for 1 year prior to a living-

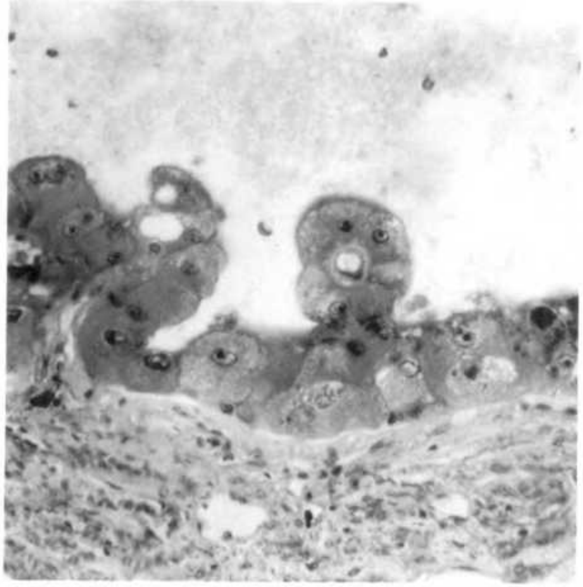

**Fig. 2** Lining of a cyst with hyperplastic and dysplastic epithelium (case no. 3). Small papillary fronds project into the lumen of the cyst. (H and E × 220).

related renal transplant in 1976. The graft was lost because of chronic rejection 3 years later and the patient remained on haemodialysis for the next 9 years. In 1988 he presented with gross haematuria localised to the left renal unit by cystoscopy. CT scan revealed bilateral renal

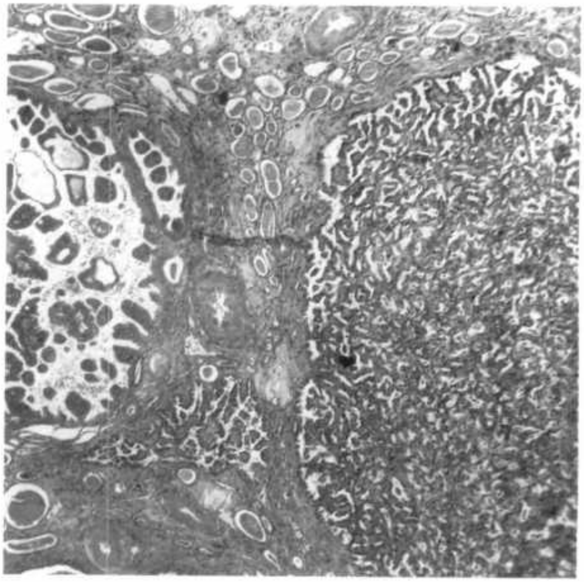

**Fig. 4** Representative low power view of histology of kidney tumours (case no. 3). Severe tubular atrophy and interstitial fibrosis are seen in the background. The tumour nodule at the left measures 1.5 mm in diameter and shows papillary fronds with severe cellular atypia similar to those in Figures 2 and 3. A small portion of a larger, elongated nodule measuring 7 × 4 mm is seen. The larger nodule has a more solid appearance, similar to clear cell carcinoma. A very small papillary tumour is wedged between the 2 larger nodules in the bottom half of the field. (H and E × 150).

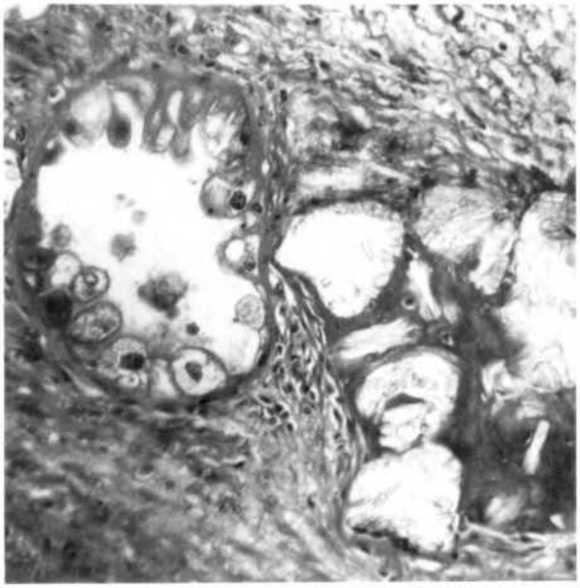

**Fig. 3** Case no. 3. Several oxalate crystal deposits surrounded by fibrous tissue are seen in the right portion of the photograph adjacent to a very small cyst lined by ballooned dysplastic tubular cells. (H and E × 150).

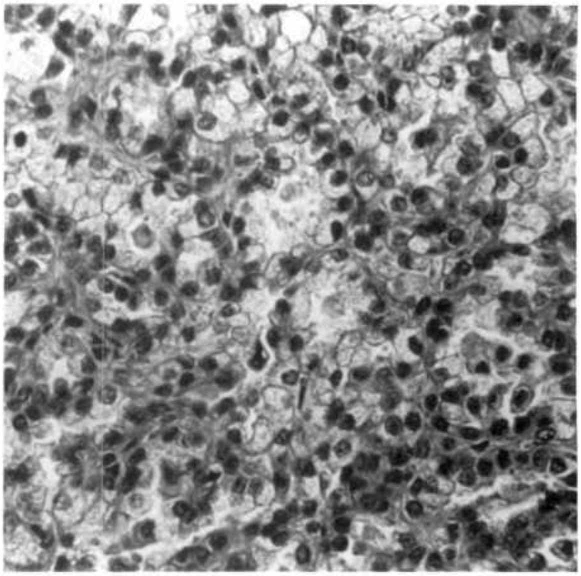

**Fig. 5** High power microscopic appearance of tumour cells from righthand side nodule in Figure 4. The histology is identical to clear cell carcinoma of the kidney but the nodule was well circumscribed. (H and E × 300).

enlargement with multiple renal lesions, solid as well as cystic, in the left kidney (Fig. 6). Pre-operative evaluation was negative for metastatic disease. Retrograde pyelography revealed no definite filling defects. A pre-operative diagnosis of renal carcinoma and ACKD was made and a left radical nephrectomy was performed. Perihilar tumour extension was apparent at the time of surgery. There was extensive cystic replacement of the left kidney, which weighed 350 g. Multiple tumours up to 1.8 cm in diameter were noted within the renal parenchyma. The perihilar lymph nodes contained metastatic renal carcinoma (Fig. 7). Morphology of the tumour nodules was variable, ranging from poorly differentiated to papillary and to clear cell renal carcinoma. His post-operative course was complicated by spontaneous caecal and sigmoid colon perforations that required total colectomy and creation of an ileostomy and mucous fistula. Intra-abdominal abscesses and gangrenous cholecystitis ensued. He eventually died from generalised sepsis. At autopsy the remaining right kidney, which weighed 380 g, was noted to contain multiple cysts ranging from 0.5 to 1.5 cm in diameter with extensive fibrosis and deposition of oxalate crystals. No tumours were identified.

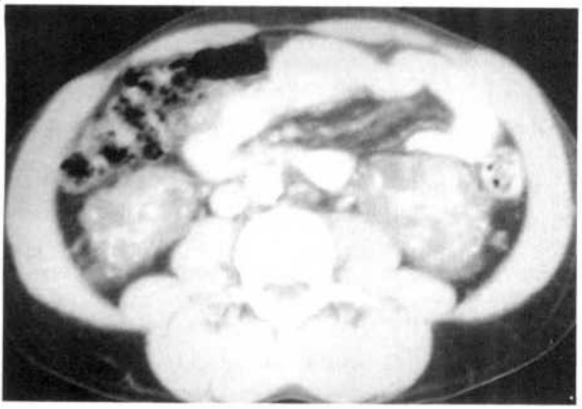

**Fig. 6** CT scan appearance of kidneys in case no. 5. Multiple cysts are seen in the renal parenchyma with an appearance and distribution similar to autosomal dominant polycystic kidney disease.

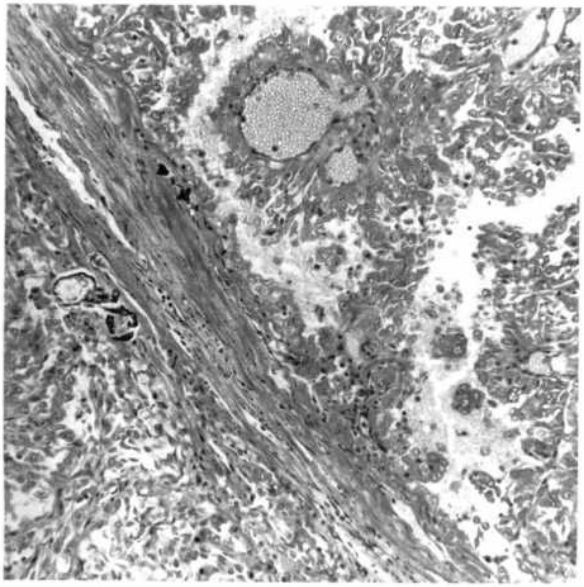

**Fig. 7** Histology of metastatic tumour in case no. 5. The invasive tumour was mostly papillary with focal areas having a spindle cell appearance. (H and E × 160).

## Discussion

### *Incidence of cystic changes*

In the series reported by Dunnill *et al.* (1977), 14 of 30 patients (47%) had pathological signs of ACKD and multiple tumours were present in 5 cases. Neither age, ethnic origin nor nature of the underlying renal disease has a statistical correlation with the incidence of ACKD (Levine *et al.*, 1984), although males are reportedly more likely than females to develop the disease (Ishikawa *et al.*, 1985).

Patients treated with peritoneal dialysis are commonly supposed to be at less risk of developing ACKD than patients undergoing haemodialysis (Beardsworth *et al.*, 1984; Jabour *et al.*, 1987; Trabucco *et al.*, 1987). However, a recent study has found the incidence to be nearly equal in the 2 groups when adjusted for the number of years on dialysis (Fallon *et al.*, 1988). It appears that the duration of dialysis correlates with the incidence of ACKD, especially after the first 3 years (Ishikawa *et al.*, 1980). Mickisch *et al.* (1984) also noted a correlation between the incidence of ACKD, the number and size of cysts, and the duration of dialysis.

ACKD may occur in the uraemic state even before dialysis begins (Bommer *et al.*, 1980; Mickisch *et al.*, 1984). Neither the severity of uraemia nor the efficacy of dialysis as measured by serum creatinine level correlates with the incidence or severity of ACKD (Levine *et al.*, 1984).

### *Effect of transplantation*

Renal transplantation may retard the development of ACKD in native kidneys compared with non-transplanted cases and can result in variable degrees of regression of cystic disease (Ishikawa *et al.*, 1983; Vaziri *et al.*, 1984). In some patients with functioning renal transplants, complete (or nearly complete) regression of cysts has been noted (Ishikawa *et al.*, 1983).

### *Incidence of neoplasia*

The incidence of renal tumours in patients with ACKD varies widely as a result of differing definitions of what constitutes ACKD (cystic replacement versus the mere presence of cysts), the method of detection (radiological, surgical or autopsy) and the problem of differentiating renal "adenoma" from adenocarcinoma. Many of these cysts and tumours are too small to be detected by CT or ultrasound imaging, resulting in lower reported incidences in radiological series (10%) than in autopsy series (25%) (Gehrig *et al.*, 1985).

Another problem is that there are no differentiating morphological characteristics between "adenomas" and renal carcinomas, either by light or electron microscopy (Bennington and Beckwith, 1975). Renal adenomas are present in about 20% of patients with ACKD but renal carcinomas (defined as tumours >3 cm in diameter) are present in only about 5% of patients (Gehrig *et al.*, 1985). At least 13 cases of metastases from renal carcinomas in patients with ACKD have been reported (Gehrig *et al.*, 1985; Basile *et al.*, 1988). Gardner and Evan (1984) reviewed published reports of adenocarcinoma in ACKD and reported that the rate of occurrence of renal carcinoma in dialysis patients with ACKD was over 30 times higher than that predicted in the general population and over 7 times higher than that seen in dialysis patients without ACKD. We agree with these authors that these high rates of incidence justify considering ACKD to be a pre-malignant lesion.

### *Pathology*

The end-stage kidney with ACKD is typically small and contracted, usually weighing less than 350 g, as compared with the larger kidneys common in autosomal dominant polycystic kidney disease. Since the distribution of cysts and bilaterality are identical in the 2 conditions, the size of the kidneys is one of the most important distinguishing features. Pathological changes in ACKD are superimposed on those of end-stage renal disease. In patients with end-stage renal failure, the cause for the patient's renal failure often cannot be determined histologically due to supervening glomerulosclerosis, tubular atrophy and fibrosis. Cysts, ranging in size from microscopic to a few centimetres in diameter, are scattered throughout the kidney. The cysts may impinge on the hilum and collecting system and may totally obliterate the parenchyma. They contain clear, mucoid, gelatinous or bloody fluid, depending on the degree of secondary haemorrhage. Although usually lined with thin atrophic epithelium, some cysts, termed "atypical" by McManus *et al.* (1980), contain a hyperplastic epithelium with a hobnail (or heaped-up) appearance. Papillary projections may be present and cytological findings range from dysplasia to frank carcinoma. Neoplasms are often multiple and bilateral. They may be papillary, arising from the lining of cyst walls, or they may be solid, with tubular, oncocytic and papillary patterns. The histological appearance varies widely (McManus *et al.*, 1980) (Fig. 4).

### *Aetiology*

One hypothesis is that ACKD represents an extreme manifestation of changes that occur with ageing of the normal kidney. Using microdissection techniques, tubular diverticula of the distal or collecting tubules have been observed in kidneys of older individuals but not in younger subjects (Baert and Steg, 1977). These findings led to the suggestion that tubular obstruction or weakening of the basement membrane supporting the tubule might cause cyst formation. Continuity between the proximal renal tubular system and some of the cysts in kidneys with ACKD has been reported (Feiner *et al.*, 1981). These studies support the hypothesis that cysts may arise from tubular obstruction, weakening in the tubular basement membrane, or increased radial growth of the tubular epithelium and basement membrane with ballooning of the tubular wall. Intratubular oxalate (commonly seen in microscopic sections of kidneys from ACKD patients), precipitated calcium, proteins or proliferation of the tubular epithelium also may mechanically obstruct the tubular lumen. However, the obstruction hypothesis does not explain the well documented regression of ACKD following successful renal transplantation (Ishikawa *et al.*, 1983; Vaziri *et al.*, 1984).

A second hypothesis is that compounds originating from the haemodialysis machine (di-2-ethylhexylphthalate (DEHP) and diphenylamine) lead to the changes seen in ACKD. Animal studies have shown that rats fed diets containing high concentrations of the plasticisers develop renal cysts (Crocker and Safew, 1984). DEHP is leached from the plastic tubing of the artificial kidney and does accumulate in the blood and tissues of dialysis patients (Baker, 1978). However, DEHP has not been proven to be a carcinogen. The association between ACKD and haemodialysis has been weakened considerably by the observation that ACKD occurs in patients undergoing peritoneal dialysis as well as in uraemic patients not receiving dialysis. These observations make the haemodialysis hypothesis much less tenable.

A third and more attractive hypothesis is that biologically active substances produced in response to the severe reduction in functioning nephron mass may be stimuli for renal cyst formation and the proliferation of renal tumours. Renal tubular cysts as well as tubular hypertrophy and hyperplasia have developed in rats undergoing $1\frac{5}{6}$ nephrectomy (Kenner *et al.*, 1985). Alternatively, biologically active substances may accumulate as a result of uraemia and be inefficiently cleared by dialysis. The polyamines (spermine, spermidine and putrescine), powerful stimulants of smooth muscle cell growth, are markedly elevated in uraemic serum and remain elevated in patients despite dialysis (Bagdade *et al.*, 1979). Even more convincing, however, are recent reports of a specific renal cyst growth factor isolated from cysts in patients with ACKD (Torrence *et al.*, 1988; Marcus *et al.*, 1989). The nature and source of such cystogenic factors remain to be determined.

### *Clinical manifestations*

In the majority of patients ACKD is asymptomatic and is discovered incidentally by renal ultrasonography, CT scanning or at autopsy. Symptomatic patients usually present with flank pain, haematuria or other signs of renal haemorrhage. Haemorrhage is usually intracystic and probably occurs from attenuated atherosclerotic vessels within cyst walls. Retroperitoneal haematoma may rarely develop (Ratcliffe *et al.*, 1983). Platelet dysfunction associated with uraemia and the use of heparin during haemodialysis may increase the risk of bleeding episodes in these patients. Renal colic may also develop secondary to calcium oxalate and matrix calculi (Bommer *et al.*, 1979).

### *Radiological findings*

Although ultrasound is commonly used for screening, CT scanning appears to be more sensitive than ultrasound in detecting small renal masses. Kidneys with ACKD can be difficult to visualise by either modality. Ultrasonographically, they usually appear small with multiple sonolucent areas representing cysts. The normal corticomedullary junction demarcation is lost. On CT scans, cysts usually range from −10 to +20 Hounsfield units, depending on their size and the degree of secondary haemorrhage within them. Our experience is that masses may be difficult to detect, even with contrast enhancement, owing to distortion of the normal renal anatomy or the presence of haemorrhage. This is illustrated by case no. 2, in which the CT scan delineated a large left renal cyst but failed to demonstrate a 3.5-cm tumour found on pathological examination.

### *Clinical management*

Given the considerable risk of developing malignancy in an end-stage kidney, we recommend that all patients being considered for dialysis (haemodialysis or peritoneal dialysis) have renal ultrasonography performed as a baseline study. Since the incidence of ACKD increases significantly after 3 years of dialysis, patients should undergo yearly renal ultrasonography after the third year of dialysis. Given that the risk of malignancy is significantly increased only in those dialysis patients who develop ACKD, yearly CT scanning is recommended in patients found to have cystic renal changes or masses by ultrasonography.

Small renal masses detected in asymptomatic patients can pose problems in management. Some authorities advocate surveillance and removal of tumours only if larger than 3 cm in diameter (Levine *et al.*, 1984). However, our experience with one case in this series as well as the literature demonstrate that small tumours may be invasive and metastasise. Although the potential for metastases in smaller tumours is statistically low, too little is known about the natural history of small renal tumours in ACKD to advocate surveillance in the patient with a small renal mass. We advise radical nephrectomy in patients with ACKD found to have small renal masses who are acceptable operative risks.

It is unclear whether contralateral nephrectomy should be performed at the time of, or subsequent to, the removal of a renal malignancy. ACKD is a bilateral disease and the contralateral kidney may harbour or later develop renal tumours. This risk must be weighed against the substantial morbidity and mortality of bilateral nephrectomy in the dialysis patient. The anephric state makes patients more prone to fluid overload, hyperkalaemia and congestive heart failure and they can become dependent on blood transfusions to maintain their haematocrit. Thus, we advise careful surveillance of the remaining kidney with yearly CT scans.

In patients with haematuria or flank pain, a CT scan is recommended as the initial diagnostic modality. If a mass is visualised, we recommend a radical nephrectomy. If no definite mass is appreciated on CT scan, renal haemorrhage can usually be managed non-operatively with blood transfusion, bed rest and observation. Angiography with selective renal arterial embolisation with autologous clot or coils should be considered in cases of persistent haemorrhage and may obviate the need for nephrectomy in patients who are poor operative risks. Persistent pain, severe haemorrhage or obstruction with infection and abscess formation are indications for nephrectomy.

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# Ureteroureterostomy and Pyeloureterostomy without Native Nephrectomy in Renal Transplantation

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Summary—A series of 23 patients, receiving full immunosuppression following renal transplantation, underwent a uretero- or pyelo-ureterostomy with ligation of the native ureter and no nephrectomy. In 5 patients this was carried out at the time of transplantation because of a short donor ureter and in 18 patients, at a median of 47 days after transplantation, following ureteric complications. With a median follow-up of 22 months, no complications have been seen in relation to the native kidney.

Ureteroureterostomy was successful in all but 3 patients. A ureteroureterostomy without native nephrectomy is a safe and effective treatment for the management of ureteric complications following renal transplantation.

The most frequent urological complications following renal transplantation are related to the ureter and published series quote rates varying from 0.9 to 29.6% (Loughlin *et al.*, 1984). Continuity of the urinary tract is usually restored by a ureteroneocystotomy. If a pyeloureterostomy or ureteroureterostomy is used as a primary procedure for restoring continuity of the urinary tract, the options available for correction of ureteric complications are limited to the use of the contralateral native ureter, a Boari flap or an ileal interposition, all of which are difficult and carry a significant morbidity. As a result, pyeloureterostomy or ureteroureterostomy are generally reserved for short donor ureters or the correction of post-transplantation urinary leaks and ureteric stenosis (Donohue *et al.*, 1975; McDonald *et al.*, 1987). Most surgeons advocate ipsilateral nephrectomy either before or at the time of ureteroureterostomy to avoid potential complications of an obstructed system in an immunocompromised patient (Corriere *et al.*, 1973; Greenberg *et al.*, 1977; Jaffers *et al.*, 1982).

We report our experience of 23 patients undergoing either pyeloureterostomy or ureteroureterostomy without a native nephrectomy.

## Patients and Methods

Five patients underwent an elective pyelo- or uretero-ureterostomy at the time of transplantation when the donor ureter had been damaged during harvesting or was too short for a direct implant (Table 1). In 18 patients a ureteroureterostomy was performed for late complications, for ureteric stenosis in 17 and a ureteric leak in 1 (Table 2). The median time from transplantation to the first corrective procedure was 47 days (range 9–1819). It was performed as a primary treatment for ureteric stenosis in 11 patients and as a secondary procedure following either failure of a ureteric reimplant in 3

**Table 1** Ureteroureterostomy at the Time of Transplantation (short ureter)

| *Cause of renal failure* | *Follow-up (months)* | *Current creatinine b (μmol/l)* |
|---|---|---|
| Polycystic kidney | 1 | Dialysis, died 1 year later |
| Hypertension | 21 | 184 |
| Reflux nephropathy | 21 | 120 |
| Glomerulonephritis | 8 | 159 |
| Diabetes | 4 | 772 |

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**Table 2** Ureteroureterostomy for Late Complications

| *Cause of renal failure* | *Onset of stenosis (days after transplantation)* | *Follow-up (months)* | *Current creatinine (μmol/l)* |
|---|---|---|---|
| (1) Ureteroureterostomy as primary procedure | | | |
| Dysplastic kidneys | 1819 | 114 | 268 |
| Chronic pyelonephritis | 311 | 93 | 200 |
| Hypertension | 41 | 38 | 105 died |
| Hypertension | 107 | 46 | 155 |
| Hypertension | 50 | 20 | Dialysis |
| Hypertension | 42 | 25 | 207 |
| Reflux nephropathy | 105 | 16 | 125 |
| Diabetes | 31 | 2 | 215 died |
| Unknown | 27 | 3 | 113 |
| Polycystic kidneys | 17 | 2 | 207 |
| Diabetes | 9 | 3 | 158 |
| (2) Ureteroureterostomy as secondary procedure | | | |
| Goodpasture's | 58 | 86 | 142 |
| Diabetes | 252 | 54 | Dialysis |
| Polycystic kidneys | 51 | 37 | 283 |
| Glomerulonephritis | 29 | 20 | 137 |
| ?Glomerulonephritis | 12 | 3 | 240 |
| Diabetes | 65 | 1 | 110 |
| (3) Ureteroureterostomy for urinary leak | | | |
| Diabetes | 44 | 32 | 185 |

or failure of transcutaneous balloon dilatation of the ureter (± endoscopic bee-sting incision of the lower ureter) in a further 3.

In all patients the diseased ureter was identified via an extraperitoneal approach and traced proximally to normal ureteric tissue. The peritoneum was opened and the native ureter identified by incising the posterior peritoneum in an area not previously disturbed by the mobilisation required for the renal transplant. The ureter was then mobilised and divided, leaving its blood supply intact, and the proximal end ligated with linen. A spatulated end-to-end anastomosis with 4/0 continuous catgut was then performed. In the first 4 patients this was carried out over a Cummins rat-tail nephrostomy tube. In the other 19 patients a 7 F 16 cm double pigtail ureteric was inserted. All patients have been followed up regularly in a specific transplant clinic. The median follow-up was 22 months (range 1 month–9½ years).

## Results

A pyelo- or uretero-ureterostomy was carried out in 23 patients and was successful in all but 3. The first 2 ureteroureterostomies leaked and were taken down to be replaced by a Boari flap. The third patient, a diabetic with ureteric stenosis, required a total of 9 procedures (including a ureteric reimplantation, a right and a left ureteroureterostomy) and was eventually cured following insertion of an ileal interposition. A further diabetic patient required 3 explorations following ureteroureterostomy for a ureteric leak. After further resuturing, the outcome was satisfactory and he has now been followed up for 2 years and 8 months.

Following transplantation, all patients were maintained on prednisolone, azathioprine and/or cyclosporin. The series included 6 diabetics and 3 patients who developed renal failure secondary to chronic pyelonephritis or reflux nephropathy. Despite this, no complications were seen following ligation of the native ureter leaving the kidney *in situ*. Two patients have died, both with normal renal function, and 3 have returned to renal dialysis, 1 as a result of vascular rejection and 2 because of chronic rejection secondary to poor drug compliance, diabetes and alcohol abuse. All patients underwent ultrasound scans of the native kidney during follow-up. Dilatation of the renal pelvis was seen in all cases.

## Discussion

The favourable outcome of long-term ligation of native ureters in transplant patients was reported in 7 cases by Baquero *et al.* (1984): 1 patient in their series, which had a follow-up period ranging from 1 month to 6 years, complained of loin pain. In the present series (with a longer follow-up), ligation of the native ureter without ipsilateral nephrectomy caused no ill effects and the patients have avoided the extra morbidity associated with nephrectomy. In only 3 cases was ureteroureterostomy unsuccessful and a fourth patient required resuturing of the anastomosis. Two of these patients were diabetic and the blood supply to their native ureters may have been compromised. Jaffers *et al.* (1982) reported results using non-absorbable sutures for elective pyeloureterostomy at the time of transplantation. Urine leakage occurred in 5/101 cases (4.9%) and late stone formation occurred along the suture line in 3/101 pyeloureterostomies (2.9%) sutured with monofilament nylon. Following these findings they changed to 7/0 prolene and 2 complications (3.1%) occurred in 63 subsequent pyeloureterostomies. In the present series all anastomoses were sutured with 4/0 catgut. Four patients, 2 of whom were diabetic, developed a urine leak. No stone formation or stenosis has occurred in relation to the anastomosis. Pyelo- or uretero-ureterostomy carried out with absorbable sutures without ipsilateral native nephrectomy is a safe and successful procedure for the treatment of ureteric complications in renal transplantation. It avoids added operative time and morbidity. No patient developed complications related to the presence of an obstructed native kidney and no stenosis or stone formation was seen at the site of the anastomosis. We therefore recommend that the native kidney is not removed when a ureteroureterostomy or pyeloureterostomy is performed for a short donor ureter or for ureteric complications following renal transplantation.

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# Renal Oncocytomas—An Australian Experience

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Summary—A review was made of 24 cases of renal oncocytoma seen between 1978 and 1989. There was considerable overlap between the clinical presentation of renal oncocytomas and renal carcinomas. Although pre-operative radiological, cytological and pathological investigations may suggest the presence of an oncocytoma, these studies cannot make a definitive diagnosis. We recommend that these tumours be treated as potential renal carcinomas until post-operative microscopic evaluation proves otherwise.

Oncocytomas are neoplasms consisting of oncocytes, which are large epithelial cells with finely granular eosinophilic cytoplasm (Fig. 1). The term "oncocytoma" was first introduced as a synonym for adenolymphoma of the salivary glands (Jaffe, 1932) and these tumours have been subsequently identified in the thyroid, parathyroid and lacrimal glands, and in the pancreas, anterior pituitary and kidney (Hamperl, 1962).

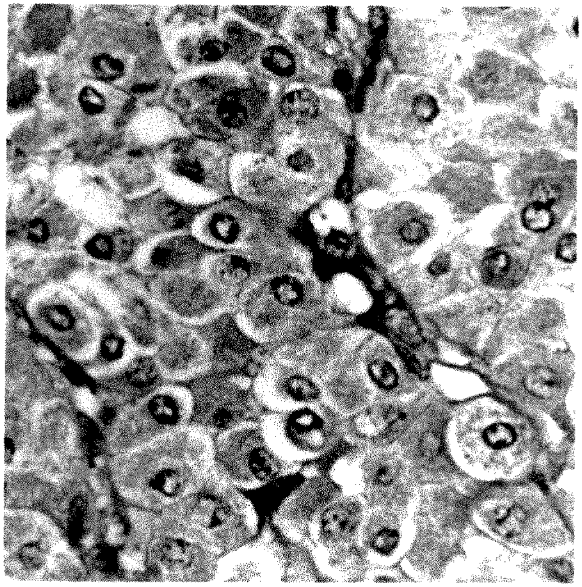

**Fig. 1** Renal oncocytoma composed of cells with abundant granular cytoplasm and uniform nuclei. (H and E ×475).

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Although the first renal oncocytoma was described by Zippel in 1942, it was not until 1976, when Klein and Valensi reported proximal tubular adenomas with oncocytic features, that this neoplasm became widely recognised as a clinical entity. Since then over 200 cases have been reported in the English literature.

Ultrastructurally, the characteristic feature of the oncocyte is the abundance of mitochondria and the paucity of all other cytoplasmic organelles (Fig. 2). Macroscopically the tumour is typically tan brown in colour, usually devoid of haemorrhage and necrosis, but it may have a prominent central scar. It is well encapsulated and rarely invades surrounding tissues.

Renal oncocytomas usually follow a benign clinical course and many authors have advocated partial nephrectomy or enucleation because of this good prognosis. All cases of renal oncocytoma seen at the Royal North Shore Hospital, over an 11-year period were reviewed retrospectively with a view to identifying any pre-operative investigations that might conclusively distinguish an oncocytoma from a renal carcinoma, and therefore make conservative renal surgery possible.

## Materials and Methods

The pathology tissue registry was searched for cases of renal oncocytoma presenting between 1978 and

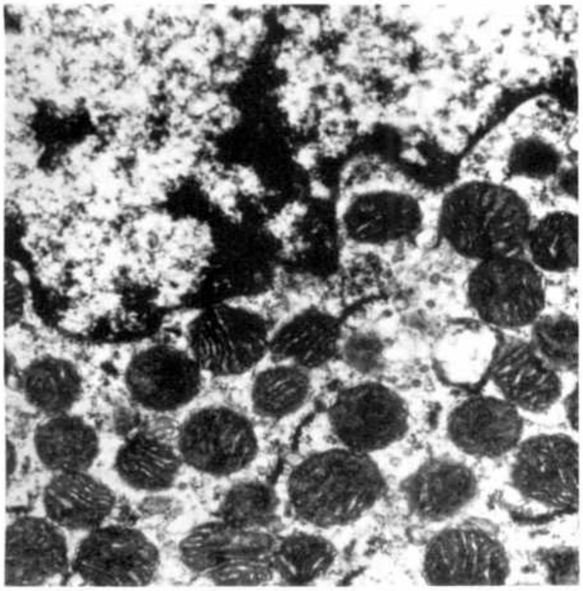

**Fig. 2** Electron micrograph of oncocyte with abundant cytoplasmic mitochondria.

1989, and 24 cases were identified. All renal carcinomas were reviewed for the years 1978 to 1984, but because of a greater awareness of the pathological entity after that date, only lesions reported as oncocytoma, or lesions suspicious of oncocytoma, were extracted from the files and reviewed from 1984 to 1989. The formalin fixed, paraffin embedded, haematoxylin and eosin stained slides were reviewed by one of us (R.P.E.). All tumours had been extensively sampled and only tumours of uniformly low histological grade and composed exclusively of oncocytes were included in the analysis. The clinical histories of the patients were subsequently reviewed, together with the pre-operative radiological and pathological studies. Complete follow-up of the patients was obtained whenever possible. The prevalence, clinical presentation and investigative findings in patients with oncocytomas were compared with those in patients with renal carcinoma.

## Results

The age and sex distribution, symptoms at presentation, pre-operative radiological and pathological investigations, surgical treatment, post-operative pathology and follow-up of each patient are summarised in the Table.

Renal oncocytomas comprised 7% of all solid renal tumours treated during the 11-year period. Urothelial tumours and angiomyolipomas were not included in the analysis. There were 14 men and 10 women (ratio 1.4:1) who ranged in age from 38 to 87 years (mean 64.8). The tumours varied in size from 1.5 to 11.5 cm (mean 4.8) and were multicentric unilaterally in 4 cases and bilateral in 1; 1 patient had had a contralateral nephrectomy 5 years earlier for a renal carcinoma.

The tumour was found incidentally in 12 patients (50%). The others presented with symptoms related to the oncocytoma, such as haematuria (6 cases), loin pain (7), loin mass (1) and anaemia (1).

The results of pre-operative intravenous urography and/or ultrasonography revealed non-specific changes of a space-occupying lesion within the kidney. These studies were of no diagnostic value in differentiating an oncocytoma from a renal carcinoma.

Eleven patients underwent selective renal arteriography pre-operatively. This revealed 7 oncocytomas with irregular neovascularisation. A hypovascular mass was identified in a further 2 cases and a spoke-wheel arrangement of vessels was seen in 1 case only. These films were reviewed (J.R.) and the diagnosis of oncocytoma could not be made conclusively in any case, even in retrospect.

Computed tomography (CT) was performed in 17 patients and identified 20 oncocytomas. Two distinct patterns were identified on the contrast-enhanced scans. In 8 oncocytomas, whose mean diameter was 2.4 cm, a homogeneous solid tumour was seen, but in 12 oncocytomas, with a mean diameter of 5.4 cm, a sharply defined lucent area was seen in the centre of an otherwise homogeneous mass. This lucent area corresponded to an area of central stellate scarring. The scans were reviewed and although the 2 patterns were identified, the overlap between the appearances of the oncocytomas and those of renal carcinomas was such that a confident diagnosis of the nature of the tumour could not be made.

Pre-operative fine needle aspiration biopsy was performed in one oncocytoma and was reported as showing a well differentiated renal carcinoma. Peri-operative frozen section was performed in a further 5 cases, giving a diagnosis of oncocytoma in 2 cases, renal carcinoma in 2 and probable oncocytoma in 1.

Pathological evaluation revealed that in 23 cases the tumour was confined to the kidney; invasion of perinephric fat was present in 1 case (Fig. 3). No other tumours breached the renal capsule. One patient had osseous metaplasia associated with an

**Table** Details of Patients

| *Case* | *Sex* | *Age (years)* | *Presentation* | *Angiography* | *CT* | *FNAB/FS** | *Surgery* | *Pathology* | *Follow-up* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 70 | Incidental | | | | Nephrectomy | 2 Oncocytomas 1.8 cm, central scar invading perinephric fat 2.1 cm | Alive and well 5 years |
| 2 | F | 79 | Haematuria | | Homogeneous | | Nephrectomy | 1.8 cm Oncocytoma | Alive and well 3 years |
| 3 | M | 38 | Loin pain | Neovascularity | | | Nephrectomy | 8 cm Oncocytoma, central scar | Alive and well 5 years |
| 4 | M | 66 | Incidental, solitary kidney | Neovascularity, tumour blush | Inhomogeneous | Renal carcinoma | Partial nephrectomy | 1.9 cm Oncocytoma | Alive and well 1 year |
| 5 | M | 80 | Haematuria, anaemia | Neovascularity, ? spoke-wheel | Central lucency | | Nephrectomy | 5 cm Oncocytoma, central scar | Died myocardial infarct |
| 6 | F | 68 | Loin pain | Hypovascular | | | Nephrectomy | 5 cm Oncocytoma, central scar | Alive and well 5 years |
| 7 | F | 87 | Incidental | | Central lucency | | Nephrectomy | 3.4 cm Oncocytoma, central scar, multicentric foci of oncocytes | Alive and well 2 years |
| 8 | F | 80 | Incidental, autopsy | | | | | 5 cm Oncocytoma | |
| 9 | F | 72 | Incidental | Hypovascular | | | Nephrectomy | 6.5 cm Oncocytoma | Died myocardial infarct |
| 10 | M | 72 | Haematuria | Neovascularity | | | Nephrectomy | 8 cm Oncocytoma, central scar | Alive and well 7 years |
| 11 | M | 72 | Loin pain, renal failure | | Homogeneous | | Partial nephrectomy | 3 cm Oncocytoma | Lost to follow-up |
| 12 | M | 48 | Incidental | | Central lucency | | Nephrectomy | 3 cm Oncocytoma, central scar | Alive and well 3 years |
| 13 | M | 70 | Incidental | Neovascularity | Central lucency | Renal carcinoma ? adenoma (FNAB) | Nephrectomy | 4 cm Oncocytoma, central scar | Died myocardial infarct |
| 14 | M | 64 | Haematuria, loin pain | Neovascularity | Central lucency | Oncocytoma | Nephrectomy | 6 cm Oncocytoma, central scar | Alive and well 5 years |
| 15 | F | 59 | Loin pain | Neovascularity × 1 lesion (L) kidney × 2 lesions (R) kidney | Bilateral lesions, central lucency | | Nephrectomy, contralateral tumour enucleations | (L) Kidney 7 cm oncocytoma, central scar, osseous metaplasia right kidney 4 cm Oncocytoma, 2 cm Oncocytoma | Alive and well 3 years |
| 16 | F | 38 | Haematuria, loin pain | | Central lucency | | Nephrectomy | 10 cm Oncocytoma, central scar | Alive and well 2 years |
| 17 | M | 63 | Incidental, solitary kidney | Neovascularity | Homogeneous | | Partial nephrectomy | 3 cm Oncocytoma | Alive and well 1½ years |
| 18 | F | 62 | Haematuria | | Central lucency | | Nephrectomy | 11.5 cm Oncocytoma, central scar | Alive and well 6 months |
| 19 | M | 76 | Incidental | | Homogeneous | Probable oncocytoma | Nephrectomy | 2 Oncocytomas, 1.6 and 1.5 cm | Alive and well 2 years |
| 20 | M | 40 | Loin pain | | Central lucency | | Nephrectomy | 4.2 cm Oncocytoma, central scar | Alive and well 4 years |
| 21 | M | 61 | Incidental | | Homogeneous | Oncocytoma | Partial nephrectomy | 2 cm Oncocytoma | Alive and well 4 years |
| 22 | F | 63 | Incidental | | | Renal carcinoma | Nephrectomy | 4 cm Oncocytoma | Died myocardial infarct |
| 23 | F | 65 | Incidental | Normal | Homogeneous | | Nephrectomy | 4 cm Oncocytoma | Alive and well 2 months |
| 24 | M | 62 | Mass | | Central lucency | | Nephrectomy | 8 cm Oncocytoma, central scar | Alive and well 6 months |

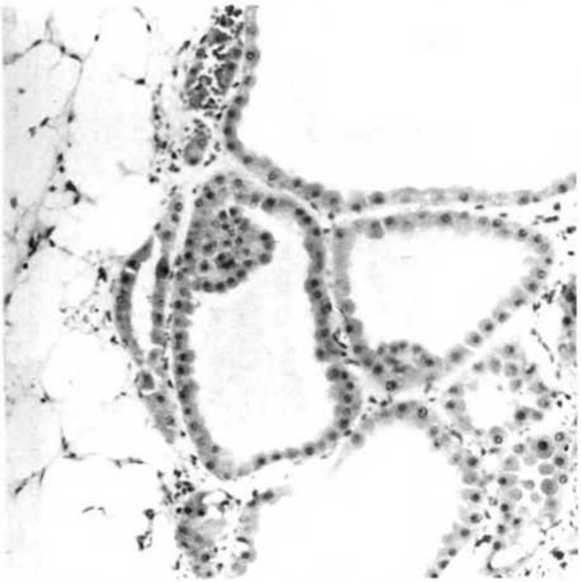

**Fig. 3** Invasion of perinephric fat by oncocytoma. (H and E × 190).

oncocytoma and another had multiple oncocytic nodules that were undetected macroscopically.

At follow-up (up to 7 years), 18 of the 24 patients were alive and well. One was lost to follow-up, 1 was found incidentally at autopsy and 4 have died of unrelated causes.

## Discussion

The results of this study confirm the overall benign behaviour of renal oncocytomas as reported by others (Klein and Valensi, 1976; Lieber *et al.*, 1981). In view of the excellent prognosis, partial nephrectomy or tumour enucleation seems to be the ideal treatment. However, pre-operative or intra-operative diagnosis is a necessary prerequisite for conservative treatment of this neoplasm.

The age and sex distribution of patients with renal oncocytoma overlaps with that of patients with renal carcinoma, being more common in men (ratio 1.4:1) and occurring in the sixth to eighth decades. Klein and Valensi (1976) indicated that oncocytomas are usually small, incidentally found renal tumours and only 1 of their 14 patients was symptomatic. In the present series, however, 50% of the patients presented with either haematuria, loin pain, anaemia or a loin mass, and the average size of the tumours was 4.8 cm. A high rate of symptomatic patients was reported by Lewi *et al.* (1985) and the median size of oncocytomas in the study by Leiber *et al.* (1981) was 4 to 6 cm. There is therefore no mutually exclusive clinical picture that will distinguish the 2 conditions.

Attempts have been made to establish the diagnosis of renal oncocytoma pre-operatively with angiography and computed tomography and the typical angiographic features were described by Weiner and Bernstein (1977). These included a well encapsulated hypervascular mass, a spoke-wheel pattern of internal vessels and a homogeneous parenchymal blush. There was no contrast medium puddling, arteriovenous shunting or grossly irregular vessels. Others have confirmed these angiographic characteristics but warned that any of these features could be present in a renal carcinoma (Ambos *et al.*, 1978). In the present series, the diagnosis of oncocytoma could not be made reliably on angiographic criteria alone. There was only 1 spoke-wheel pattern (Fig. 4) and 7 of 11 cases showed gross irregular neovascularisation (Fig. 5) indistinguishable from renal carcinoma.

Levine and Huntrakoon (1983) described the CT features of renal oncocytomas. The mean size of the lesions in their series was 2.6 cm and the features described included a distinct margin, smooth contour and a homogeneous appearance on contrast-enhanced scanning. These features, however, are not pathognomonic of oncocytomas, since

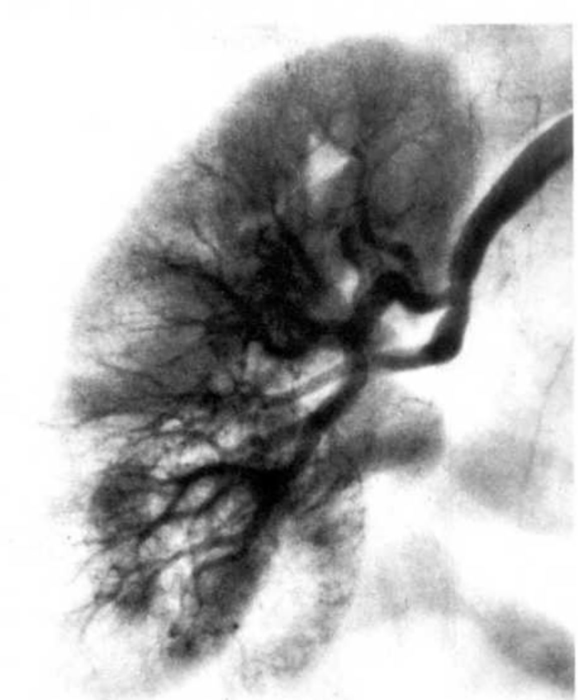

**Fig. 4** Renal arteriogram identifying lower pole oncocytoma with spoke-wheel pattern of internal vasculature.

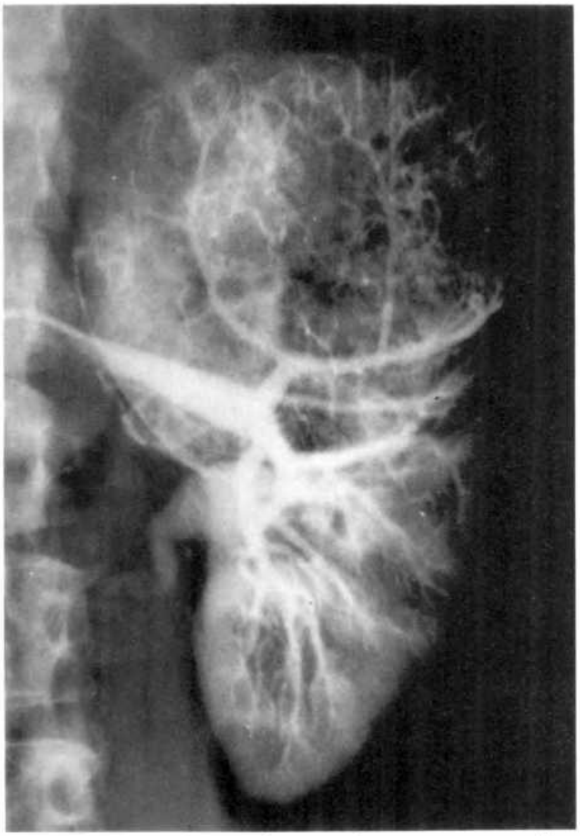

**Fig. 5** Renal arteriogram of upper pole oncocytoma revealing gross irregular neovascularisation.

small renal carcinomas can show identical patterns (Figs 6 and 7). With larger tumours the central scar becomes more prominent (Quinn *et al.*, 1984) but this feature is insufficient to differentiate an oncocytoma from a renal carcinoma with central necrosis (Figs 8 and 9).

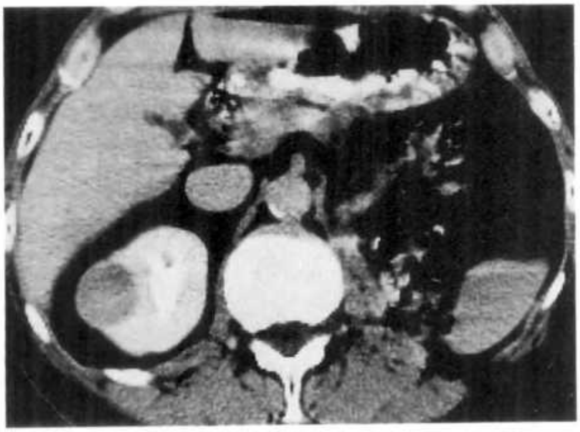

**Fig. 6** Contrast-enhanced CT scan of small oncocytoma in solitary right kidney.

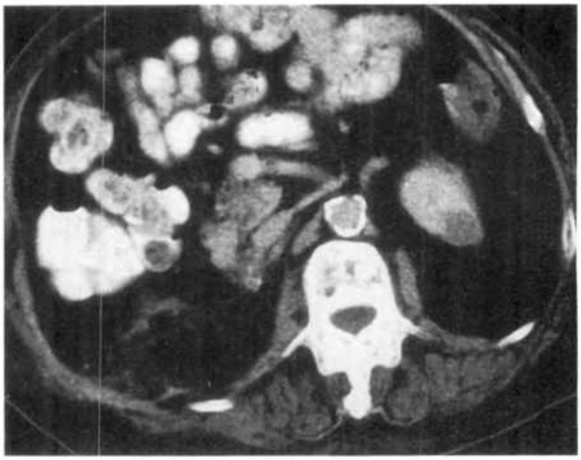

**Fig. 7** Contrast-enhanced CT scan of small renal carcinoma in left kidney.

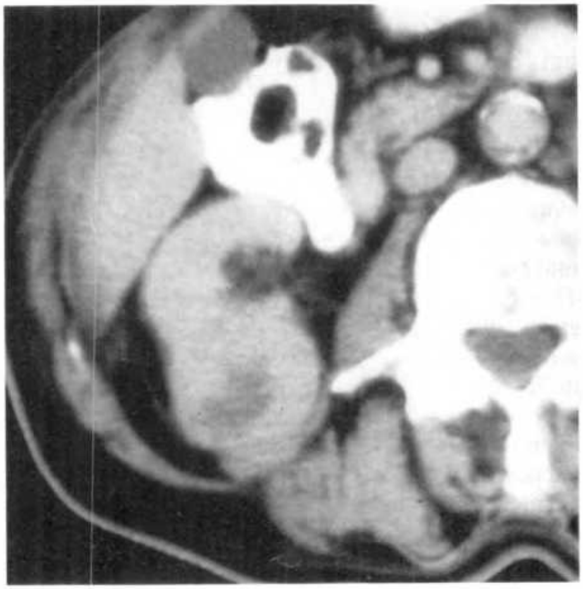

**Fig. 8** Contrast-enhanced CT scan of large oncocytoma with central lucency corresponding to a fibrous scar.

Pre-operative aspiration biopsy and intra-operative frozen section have been used successfully in some cases. Alanen *et al.* (1985) correctly diagnosed an oncocytoma in 2 of 7 cases using fine needle aspiration biopsy and Nguyen *et al.* (1985) were successful in 2 of 3 cases. However, because of the cytological similarity between oncocytoma and well differentiated granular cell renal carcinoma, and because some carcinomas focally have areas closely resembling oncocytoma, definitive diagnosis is dependent on thorough sampling of the tumour. In the present series, the single fine needle aspiration and 2 of the 5 frozen section examinations gave

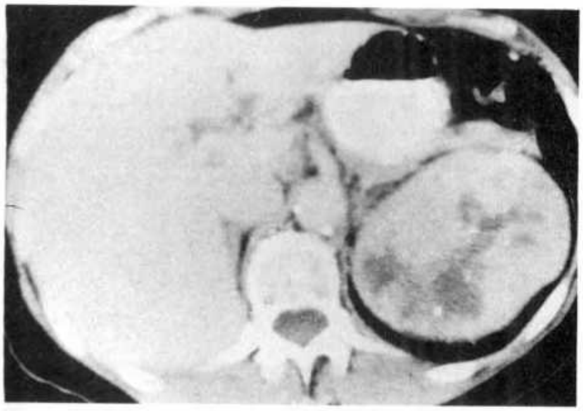

**Fig. 9** Contrast-enhanced CT scan of large renal carcinoma with central necrosis.

false results. Even in those cases where the diagnosis of oncocytoma was suggested by frozen section, it was felt that definitive diagnosis should be deferred until the tumour could be more thoroughly sampled.

The experience in Australia in general is that oncocytomas behave in a benign fashion. However, a recent study has shown that staining renal oncocytomas with anti-renal carcinoma monoclonal antibody 5F4 (Kochevar and Coffield, 1989) has identified areas of anaplastic oncocytic cells that were not initially identified on routine staining. This, together with flow cytometric data (Rainwater *et al.*, 1986) showing that most oncocytomas have some aneuploid and tetraploid populations, may indicate that a more malignant course may be expected from these atypical clones even if found in minute foci. This may explain why some oncocytomas have been reported to spread to perinephric fat (Rodriguez *et al.*, 1980; Lieber *et al.*, 1981), renal vein (Lieber *et al.*, 1981), regional lymph nodes (Lieber *et al.*, 1981; Engel *et al.*, 1987), bone (Lewi *et al.*, 1985; Jockle *et al.*, 1987), brain, lung, peritoneal cavity (Lewi *et al.*, 1985) and liver (Jockle *et al.*, 1987). As a result of the similarity between oncocytes and granular cells, the presence of oncocytic foci within renal carcinomas and the heterogeneity of oncocytomas themselves, routine histological techniques may not always be accurate in determining either the nature or the malignant potential of the tumour.

Uncertainty about the pre-operative diagnosis of oncocytoma means that this tumour should be treated as a potential renal carcinoma until post-operative pathological evaluation proves otherwise. The high rate of multicentricity in this series also tends to preclude partial nephrectomy as a therapeutic option, even if the diagnosis could be ascertained pre-operatively. Apart from cases of tumour in a solitary kidney or bilateral tumours, we recommend radical nephrectomy for all solid renal neoplasms, with appropriate follow-up.

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# Prognostic Factors in the Conservative Treatment of Ureteric Stones

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Summary—A prospective study was made of 125 ureteric stones in order to detect factors which would predict the successful outcome of conservative treatment. The factors studied were the duration of pain prior to presentation, pyuria, haematuria, surface regularity of the stone and the degree of obstruction as seen radiologically.

In stones $\leq 10$ mm in size, conservative treatment was successful when the duration of pain was $<30$ days (39/45), when there was no significant pyuria (53/82), when the stones had an irregular surface (44/65) and when obstruction was only partial (55/88). Since most of these factors were interactive, further statistical analysis showed that duration of pain was the only significant factor in predicting the outcome of conservative treatment.

In stones $> 10$ mm in size these factors had no predictive value and only 2/23 were passed spontaneously on conservative treatment.

With the advent of new endoscopic procedures for the treatment of ureteric stones there is a temptation to interfere surgically even in the absence of strong indications. Sandegard (1956) reported that stones $<4$ mm in diameter had passed spontaneously within 6 weeks in 93% of patients with lower ureteric stones and in 81% of patients with upper ureteric stones and calculi measuring between 4 and 6 mm had passed spontaneously in 50% of cases. Ureteroscopy cannot be described as a totally safe procedure, especially in the hands of the untrained, and extra corporeal shockwave lithotripsy (ESWL) is still not available in many urological centres. Although the size of a ureteric stone is the decisive factor in determining the success of conservative treatment, small stones which fail to progress on follow-up are frequently seen. The aim of this study was to establish factors (other than the size of the stone) which might predict a successful outcome following conservative treatment of ureteric stones.

## Patients and Methods

All patients presenting with ureteric colic underwent the following investigations: urine analysis, urine culture, complete blood count, blood urea, electrolytes and intravenous urography (IVU). Patients with ureteric stones of any size at any level were included in the study, with the exception of those who needed urgent surgical intervention. Indications for immediate surgery were fever with significant pyuria, severe repeated intractable pain unresponsive to analgesics and non-visualised kidneys on delayed films (up to 24 h). The remaining patients had 125 ureteric stones which were divided into 2 groups. Group A included 102 stones $\leq 10$ mm in size and group B comprised 23 stones $>10$ mm. (Size was expressed as the maximum diameter of the stone measured on plain X-ray). Patients in both groups were treated conservatively by antispasmodics, analgesics and liberal oral fluids. They were seen again after 6 weeks and underwent a KUB. Success on this conservative treatment was defined as either progression of the stone down the ureter as seen on plain X-ray or

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spontaneous passage of the stone *per urethram*. If conservative treatment was not successful, patients were advised to undergo endoscopic surgery (or open surgery if they were experiencing severe frequent pain).

The factors studied in both groups were the duration of pain prior to presentation, the presence of pyuria, the severity of haematuria, the surface regularity of the stone as seen on KUB and the degree of ureteric obstruction on IVU. Data were analysed using chi-squared statistics (with Yates correction when needed) and SPSS statistical package; 5% was chosen as the level of significance.

## Results

All of the stones which moved down the ureter within 6 weeks from the time of presentation were eventually passed spontaneously.

### *Group A*

This group included 102 ureteric stones $\leq 10$ mm (Table 1).

*Duration of pain prior to presentation.* When the duration of pain was $<30$ days, conservative treatment was successful in 39 stones and surgery was needed in only 6. When the duration of pain exceeded 30 days, 36 stones required surgery compared with 21 which were successfully passed on conservative treatment ($P < 0.05$).

*Pyuria.* In the absence of significant pyuria (*i.e.* when urine analysis showed $<10$ pus cells/HPF), conservative treatment was successful in 53 stones as compared with 29 which needed surgery. However, with significant pyuria ($>10$ PC/HPF), 13 stones needed surgery and only 7 were successfully passed on conservative treatment ($P<0.05$).

*Haematuria (red blood cells/HPF on urine analysis).* With $<100$ RBC/HPF, 45 stones were conservatively treated and 35 required surgery. With $>100$ RBC/HPF, 15 stones were conservatively treated and 7 required surgery. The difference between the 2 groups was not significant.

*Stone Surface.* In stones with a smooth surface, conservative treatment was successful on 16 occasions and 21 stones needed surgery. In the case of stones with an irregular surface, 44 were successfully treated conservatively and 21 needed surgery ($P<0.05$).

*Obstruction on IVU.* When ureteric obstruction was partial, 55 stones were successfully treated conservatively and 33 needed surgery. With complete obstruction, only 5 stones were conservatively treated compared with 9 that required surgery ($P<0.05$).

**Table 1** Ureteric Stones $\leq 10$ mm

| *Factors* | *Successful conservative treatment* | *Surgical treatment* |
|---|---|---|
| *Duration of pain* (days) | | |
| $<30$ | 39 | 6* |
| $>30$ | 21 | 36* |
| *Urine analysis* | | |
| (a) Pus cells/HPF | | |
| $<10$ | 53 | 29* |
| $>10$ | 7 | 13* |
| (b) Red blood cells/HPF | | |
| $<100$ | 45 | 35† |
| $>100$ | 15 | 7† |
| *Stone surface* | | |
| Smooth | 16 | 21* |
| Irregular | 44 | 21* |
| *Radiological obstruction* | | |
| Partial | 55 | 33* |
| Complete | 5 | 9* |

*$P<0.05$ = Significant. †$P>0.05$ = Not significant.

**Table 2** Ureteric Stones $>10$ mm

| *Factors* | *Successful conservative treatment* | *Surgical treatment* |
|---|---|---|
| *Duration of pain* (days) | | |
| $<30$ | – | 8* |
| $>30$ | 2 | 13* |
| *Urine analysis* | | |
| (a) Pus cells/HPF | | |
| $<10$ | 1 | 16* |
| $>10$ | 1 | 5* |
| (b) Red blood cells/HPF | | |
| $<100$ | 2 | 16* |
| $>100$ | – | 5 |
| *Stone surface* | | |
| Smooth | 1 | 14* |
| Irregular | 1 | 7* |
| *Radiological obstruction* | | |
| Partial | 1 | 15* |
| Complete | 1 | 6* |

*$P>0.05$ = Not significant.

Since most of these factors could have been interactive in the same patient, the most significant of them (duration of pain) was further studied individually with the other 4 factors, *i.e.* pyuria, haematuria, stone surface and obstruction on urography. No significant difference was found between the number of patients who had successful conservative treatment and those who needed surgery ($P > 0.05$).

### *Group B*

Only 2/23 stones > 10 mm were successfully treated by the conservative method; the remainder needed surgery (Table 2). The 5 factors were of no predictive value in this group.

## Discussion

With the introduction of ureteroscopy, ESWL and lasers in the last decade, most ureteric stones can now be treated successfully (Lingeman *et al.*, 1987; Coptcoat *et al.*, 1988; Tolley, 1989). However, these sophisticated methods of treatment are too expensive to be used in many urological centres, especially those of the Third World. Most of these minimally invasive procedures are still performed under general anaesthesia and they are not completely free of complications. In unfit and high risk patients, it might be safer in selected cases to adopt a conservative regime with close surveillance in the hope that the stone will pass spontaneously. The size of the stone is the most decisive factor in the outcome of conservative treatment. Nevertheless, small stones which might be expected to pass spontaneously often fail to do so even after prolonged conservative treatment. It is for these reasons that the present study was initiated in an attempt to establish factors that would predict success with conservative treatment.

Sandegard (1956) reported that within 6 weeks, 93% of lower ureteric stones and 81% of upper ureteric stones measuring <4 mm would pass spontaneously, as would 50% of stones in any part of the ureter if they measured between 4 and 6 mm. We therefore assessed the results of conservative treatment after a 6-week period. We also found that if there was radiological evidence of progression of the stone down the ureter at this time, the stone would almost invariably be passed spontaneously. Stones which did not progress failed to pass spontaneously and needed surgical intervention.

We divided the stones into 2 groups; those ≤10 mm and those >10 mm. The 5 factors were studied in each group. In the first group, when the duration of pain at presentation was <30 days, conservative treatment was successful in 39/45 stones; if the duration of pain exceeded 1 month, surgery was needed in 36/57 stones ($P < 0.05$). This may be because the initial vigorous ureteric contractions which encouraged progression of the stone gradually became weaker. Duration of pain was the most determinant factor in this study.

In the absence of significant pyuria (<10 PC/HPF), conservative treatment was successful in 53/82 stones. When there was significant pyuria (>10 PC/HPF), 13/20 stones needed surgery ($P < 0.05$). Rose *et al.* (1975) suggested that infection caused inhibition of ureteric peristalsis. However, the number of red blood cells on urine microscopy was not a significant factor in deciding the outcome of conservative treatment in this study.

Stones with an irregular surface were successfully treated conservatively on 44/65 occasions. Of 39 stones with a smooth surface, 21 required surgey and 18 were treated conservatively ($P < 0.05$). Unlike stones with a smooth surface, those with an irregular surface seldom become completely impacted and urine finds its way around the surface to the distal ureter, ensuring better flushing of the ureter and helping progression of the stone. It is also possible that the irregular surface may stimulate peristalsis by causing more irritation to the ureteric wall. It is equally true that complete obstruction by stones will cause overdistension of the proximal ureter and lead to peristaltic inhibition after initial stimulation of the smooth muscle (Rose and Gillenwater, 1973). Webb (1988) demonstrated experimentally that the paralysed overdistended ureter regains peristalsis after drainage by nephrostomy. With partial obstruction, proximal ureteric overdistension is avoided and vigorous proximal peristalsis encourages progression and total expulsion of the stone. This may be why 55/88 stones in this study were successfully treated conservatively when obstruction was partial and 9/14 stones ($P < 0.05$) needed surgery when the obstruction was complete.

Although the above factors were studied individually in our patients, more than one factor might have been operating at any one time. We therefore chose the most significant factor (duration of pain) and studied its effect together with each of the other 3 apparently significant factors (pyuria, stone surface and obstruction as seen on IVU). Statistical analysis using chi-square (with Yates correction when necessary) showed that none of the 3 factors was significant in predicting the outcome of conservative treatment. We therefore concluded that the duration of pain was the only factor of significance operating in our patients at all times.

In the second group of stones (> 10 mm), conservative treatment failed on 21/23 occasions. None of the factors was statistically significant.

Delay in surgical intervention could be criticised because of the adverse effect of increasing pelviureteric pressure on kidney function. However, Vaughan *et al.* (1970) showed that this increase was short-lived. Deterioration in kidney function was shown experimentally to be due to arteriolar constriction in response to partial obstruction and normal function was regained after 28 days' obstruction (Leahy *et al.*, 1989). All of our patients underwent intravenous urography 6 weeks after spontaneous passage of stones or surgical treatment and complete radiological recovery was confirmed.

It was concluded that, in patients with ureteric stones ≤ 10 mm, the only factor which can help to predict the outcome of conservative treatment is the duration of loin pain at presentation. The chances of success with conservative treatment are high if the duration of pain is < 30 days.

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# Lower Urinary Tract Reconstruction in Patients with Bladder Exstrophy after Failed Primary Treatment in Early Childhood

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Summary—The results of neonatal surgery for bladder exstrophy are not very satisfactory. A significant percentage of patients present in later childhood or adolescence for correction of their residual deformities.

We have reconstructed 26 patients, correcting their entire urogenital and cosmetic deformity in a one-stage procedure. The results show that one-stage total reconstruction is possible and is preferable to serial correction of the various individual abnormalities. The principles of surgical reoperation in adolescence are the same as those now established for the primary correction in neonatal life.

Bladder exstrophy is not a common problem but it is perhaps the most major urogenital and cosmetic deficit compatible with life that presents for urological attention. The principles of early neonatal surgery have been established for many years, notably as a result of the work of Jeffs and of Duckett, reviewed recently by Snyder (1990). The aim is to close the bladder and prostatic urethra, the pelvic ring and the anterior abdominal wall within the first few days of life and then correct the remainder of the defects in one or more stages electively when the child has grown a little.

Although the principles have been established and the technique repeatedly described for many years, a significant number of children present later in childhood or in adolescence with major residual problems that require further corrective surgery.

There is a point of view that further surgery is best staged to correct individual problems one at a time. We present our experience with 26 patients and suggest that one-stage total reconstruction is not only possible but preferable.

## Patients and Methods

Patients who were being followed up elsewhere and those who had undergone only partial reconstruction were excluded from the series. The study group then comprised 26 patients (17 male and 9 female, with an age range of 4–36 years and a mean of 19 years) in whom a total one-stage correction of their urogenital and cosmetic problems was attempted. The majority of patients had undergone urinary undiversion, augmentation or substitution cystoplasty, urethroplasty, bladder neck reconstruction, chordee correction and phalloplasty, or genitoplasty in female patients, and half had undergone implantation of an artificial urinary sphincter (Table 1). At the end of the operation all abdominal wall and genital scar tissue that had not previously been excised was excised and the abdominal wall and genital skin were reconstructed.

## Results

The findings at operation were almost universally the same. With the exception of 1 patient, the pelvic ring was deficient anteriorly and the overlying skin was densely scarred with separation of the pubic hair-bearing skin on each side. There was

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**Table 1** Procedures Performed during the One-stage Reconstruction

| *Procedures* | *Males (17)* | *Females (9)* |
|---|---|---|
| Cystoplasty | 17 | 9 |
| Urethroplasty | 12 | 9 |
| Bladder neck reconstruction | 17 | |
| Implantation of artificial sphincter | 8 | 4 |
| Undiversion | 10 | 8 |
| Chordee correction | 11 | N/A |
| Glansplasty/phalloplasty (male) | 15 | N/A |
| Genitoplasty (female) | N/A | 6 |

dense scarring of the genitalia, with a deformed and splayed glans penis in male patients and residual epispadias. Urethrocutaneous fistulae were common. No sooner was the abdominal skin incised than the urinary tract was found, unless the patient had previously undergone cystectomy. The bladder was small, thick-walled and the bladder neck and prostatic urethra (in males) were splayed open with a rather thin tenuous closure anteriorly. Most patients also had marked chordee and the urethra was dorsally sited on the penile shaft. Female patients usually had genital prolapse if they had previously been treated for introital stenosis, or stenosis if they had not. Rectal prolapse and either an enterocele or a rectocele were also common in female patients.

The results of surgery are shown in Table 2. Twenty patients (76%) were continent of urine and had a satisfactory correction of their other abnormalities after the one-stage procedure without complication. Six other patients had a complication requiring surgical treatment before they too had a satisfactory result; 2 of these complications were not urological.

**Table 2** Results of One-Stage Reconstruction

| | *After initial operation* | *After treatment of complications* |
|---|---|---|
| Continent, voiding spontaneously | 13 } 76% | 16 |
| Continent, voiding by CISC | 7 | 10 |
| Complications | 6–24% | — |
| Infections of AUS—removed and replaced | 2 | |
| Revision of urethroplasty | 1 | |
| Fistula to abdominal wound* | 1 | |
| Obstructing "valve" in ileal urethra resected | 1 | |
| Intestinal obstruction—adhesions | 1 | |
| Breakdown of abdominal repair (partial) | 1 | |

*closed spontaneously
CISC = Clean intermittent self-catheterisation.
AUS = Artificial urinary sphincter

## Discussion

Two aspects of these findings merit discussion: firstly, the implications for the way primary surgery is performed and, secondly, the question as to whether such surgery should be staged or carried out as a one-stage procedure.

The implications of our findings for the way in which primary surgery is performed are (1) that the prostate and bladder neck need to be fully mobilised to allow proper closure of the prostatic urethra, bladder neck and bladder and to allow these structures to be dropped back fully into the pelvis; (2) that bladder neck reconstruction cannot be expected to be maintained in the face of a thick-walled, small capacity bladder which tends to pull the bladder neck reconstruction open; (3) that urethral closure should not be obtained in young male children at the expense of urethral length and neglect of the penis. Essentially, all of these problems arise because of rather timid surgery leading to closure without full mobilisation.

When neonatal surgery gives the possibility of closure of the pelvic ring in addition to an attack on the urogenital problem, it is likely that a more adequate urinary tract closure will be achieved and the best opportunity is also given for getting the maximum possible length of the penis. When the pelvic ring is not closed it is still important to achieve adequate mobilisation of the prostate and bladder neck area from the so-called inter-symphysial band to allow satisfactory closure anteriorly rather than being just pulled together, giving a rather tenuous anterior wall. The prostatic urethra must also be separated from the penile urethra in males to allow the prostate to be dropped back and, where possible, to place the urethra when subsequently closed on to the ventral aspect of the penis after correction of the genital deformity.

In girls the same principles apply.

The question of one-stage versus multi-stage surgery depends partly on the inclination of the patient. Some patients wish only to have one aspect of any residual problem corrected (usually the genital problem) because they find that intolerable, whereas they will tolerate other disabilities without complaint. Other patients want everything corrected. Assuming that this is a reasonable proposition, the question of one-stage versus multi-stage surgery arises. Although it may seem reasonable to correct the cosmetic, urological and genital problems in a staged fashion (and many surgeons prefer to do this), there are considerable advantages in dealing with everything at once. The first and most obvious advantage is that one does not run the risk of damaging what was achieved in stage 1 when one comes to do stage 2. More importantly, there are specific advantages, the most important being that, conceptually at least, a surgeon is more inclined to perform an adequate procedure when *everything* has to be taken down and put together again, thereby avoiding the temptation to do something less than satisfactory to avoid damaging a structure one is intending to leave alone. Possibly the best example of this is failure to correct chordee in an attempt to avoid surgery on the urethra.

Other advantages of a single-stage procedure are (1) that an augmentation cystoplasty, by reducing the intravesical pressure and bladder wall tension, helps to maintain a bladder neck reconstruction; (2) that if a bladder neck has been reconstructed, then by reducing its calibre the results of subsequent artificial sphincter implantation (assuming this is necessary) are improved; equally the presence of an AUS cuff helps to maintain the bladder neck reconstruction; (3) that urinary undiversion (where relevant), by allowing urethral voiding, also improves the patency of the urethroplasty as far as ejaculation is concerned in male patients; (4) that urethroplasty and ventral placement of the urethra help to maintain chordee correction. These are examples of how correction of one abnormality helps to maintain the correction of another; hence the reason why we prefer a one-stage procedure, in addition to the obvious psychological advantage to the patient.

Most of the more difficult problems in secondary reconstruction after failed primary treatment in childhood occur in patients who still have a wide open pelvic ring. In male patients this leads to a short, stubby penis. In female patients it leads to an inadequate pelvic floor and prolapse. If the gap between the pubic bones is more than a few centimetres and the child more than a few years old it is not usually possible to correct the problem, although in younger children an anterior pelvic osteotomy might allow closure to be achieved. When this is not possible there is little that can be done in males to lengthen the short, stubby penis and little that can be done in females to correct the problems of prolapse. Undoubtedly prolapse problems are made worse by an over-enthusiastic enlargement of the introitus before puberty and for this reason we think that introital surgery should be deferred until puberty, when the state of the pelvis can be more adequately assessed.

Specific surgical techniques have not been discussed in this report because most salvage procedures simply make use of the best available tissues for cystoplasty, urethroplasty and genitoplasty. Suffice it to say that an adequate supply of tissue is required. In most male patients something is usually available, if not the ideal tissue, for these various techniques, but in female patients who have had their bladder removed there is often difficulty in reconstructing an adequate urethra.

The best way of avoiding these residual problems—the very short penis in males, the severe prolapse in females and the difficulties in delayed reconstruction—is by adequate mobilisation and closure of the urogenital tract and the pelvis and the abdominal wall in early neonatal life.

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# Management of Acute Retention of Urine: A Reappraisal

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Summary—Our standard policy for the management of retention of urine due to prostatic hypertrophy is that the patient is catheterised and sent home, later to be seen and assessed in the Out-patient Department where he is given an admission date for operation. A detailed audit of 166 patients cared for in this way is presented and the results compared with those in 25 patients who remained in hospital in the interval between catheterisation and operation and in 402 patients not previously catheterised. Although the mortality rate was significantly higher in the retention group (3.3 vs 0.25%), we feel that this is a reflection of the fitness of the patients with retention rather than a consequence of the management policy. The advantages of the "catheterise and send home" policy are discussed.

It is now 10 years since our "catheterise and send home" policy for the management of acute retention of urine was first described (Higgins *et al.*, 1981). By avoiding the need to admit some 150 emergency cases each year, this policy continues to be a major factor in allowing the use of a booking system for all admissions rather than a waiting list. A review at this stage seemed appropriate in order to ensure that this policy continued to be safe and acceptable to patients, particularly in view of the intensified pressure on beds now that 2 consultants rather than 1 are dealing with the urological case load from a population of over half a million.

## Patients and Methods

A detailed audit was performed in a consecutive series of 593 transurethral prostatectomies performed over a 14-month period from July 1987 to September 1988. The management of patients presenting with retention of urine was essentially the same as previously described. After catheterisation either in our Accident Unit, at another hospital, by the General Practitioner or the District Nurse, the patients went home or, if already at home, stayed there with arrangements made to attend the next Urological Out-patient Clinic. There, any necessary investigations were ordered and unless there was some contraindication to operation, such as a recent myocardial infarction, the patient was offered an admission date, usually to come in either on the day of or the day before operation. Exceptions were (1) those with no previous history of prostatic symptoms, who were usually admitted for a day in order to have a trial without the catheter and (2) those who were physically and/or mentally so unfit that operation was contraindicated and for whom long-term catheter drainage was the only solution. The latter group was very small. Patients sent home with a catheter were put in touch with a District Nurse who made regular visits and dealt with any minor catheter problems.

Patients who developed retention of urine while already in hospital were not necessarily sent home; if a space was available on the operating list they were transferred to the urological ward and treated surgically. The only patients with acute retention admitted directly to the ward were those with significant renal impairment or with haematuria and clot retention. Patients in the former group were usually discharged with a catheter for later

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readmission when it became clear that renal function was improving.

The type of anaesthetic used depended on the choice of the anaesthetist; approximately half of the patients were operated on under general anaesthesia and half under spinal anaesthesia. Antibiotics were given prophylactically only to those with cardiac valve problems or recent joint implants. Other procedures such as resection of bladder tumour, litholapaxy, circumcision, bilateral orchiectomy or hernia repair were carried out as necessary under the same anaesthetic.

**Table 1** Results

| | *Non-retention* | *Retention* |
|---|---|---|
| No. of patients | 402 (67.8%) | 191 (32.2%) |
| Mean age (years) | 67.97<br>(range 45–91) | 71.36*<br>(range 49–88) |
| Mean post-operative stay (days) | 4.6<br>(range 2–38) | 5.9*<br>(range 3–33) |
| Mean weight resected (g) | 22.1<br>(range 3–91) | 30.8*<br>(range 4–135) |
| Carcinoma prostate | 14.2% | 20.4%† |
| Blood given | 10.4% | 13.6%‡ |
| Deaths | 1 (0.25%) | 6 (3.3%)§ |

* Differences significant ($P<.001$) ($t$ test).
† Difference of borderline significance.
‡ No significant difference.
§ Difference significant ($P<.01$) ($t$ test).

**Table 2** Patients' Response to Catheter

| | |
|---|---|
| Prefer it | 3 |
| Neutral | 55 |
| Unpleasant | 48 |
| Very unpleasant | 0 |

## Results

Details of patients and operations are given in Table 1. Of the patients with retention, 166 (87%) had been catheterised and sent home; 25 (13%) had remained in hospital from the time of catheterisation to the time of operation. Ten of the latter group were catheterised prior to immediate admission to the urological ward, 4 in a surgical ward, 8 in medical wards and 1 each in neurosurgical, orthopaedic and psychiatric wards. The first 106 patients to be catheterised and sent home were asked, on admission to hospital, their opinion of the catheter and were given the choice of 4 responses (Table 2).

The duration of catheter drainage varied from 1 day to 10¼ years. Six patients had been catheterised for longer than 1 year; these were all patients whose General Practitioner had initially decided that referral to hospital was not appropriate because of their poor general health, the change of mind being prompted either by the patient having catheter problems and/or by a realisation that surgical intervention could now be safely undertaken. Excluding these 6 patients, the mean duration of catheter drainage was 7.1 weeks, 7.84 weeks in those patients catheterised and sent home, and 2.36 weeks in those kept in hospital (range 1 day–14 weeks).

All patients were followed up for at least 6 weeks. Those who failed to attend the Out-patient Clinic were traced via their General Practitioner.

There were 7 deaths (Table 3), giving an overall mortality rate of 1.18%. Only 1 of these patients had not been catheterised pre-operatively (mortality rate in this group 0.25%) and of those catheterised, 3 had been sent home with a catheter (mortality rate 1.8%) and 3 had remained in hospital (mortality

**Table 3** Analysis of Deaths

| *No of patients* | *Age (years)* | *Interval between operation and death (days)* | *Weight resected (g)* | *Histology* | *Blood given at or after operation (units)* | *Cause of death* |
|---|---|---|---|---|---|---|
| 1 | 72 | 6 | 13 | Carcinoma | 0 | Pulmonary embolism |
| 2 | 80 | 1 | 38 | Benign | 0 | Hepatoma and secondaries |
| 3 | 73 | 35 | 33 | Benign | 2 | Cerebrovascular accident and bronchopneumonia |
| 4 | 75 | 8 | 35 | Benign | 0 | Renal failure and bronchitis |
| 5 | 79 | 5 | 12 | Benign | 0 | Myocardial infarction |
| 6 | 83 | 1 | 40 | Benign | 0 | Myocardial infarction |
| 7 | 83 | 17 | 20 | Carcinoma | 2 | Bleeding duodenal ulcer |

Patients 1 to 6 were catheterised for retention of urine. Patients 1 and 3 were catheterised in a medical ward and kept in hospital until operation. Patient 2 was catheterised and admitted immediately to the urological ward. Patients 4, 5 and 6 were catheterised and sent home. Patients 1 and 7 were discharged 3 days post-operatively and died at home. Patient 3 died in a medical ward. Patient 7 was also subjected to bilateral orchiectomy.

rate 12%. The 3 patients who died post-operatively, having been catheterised and sent home, had all been subjected to catheter drainage for between 2½ and 3 weeks. The duration of catheter drainage in those who remained in hospital until operation and subsequently died varied from 1 day to 2 weeks. There were no deaths in the interval between the patients being given an admission date and admission to hospital.

Post-operative urinary infection or bacteraemia did not appear to be a factor in causing death in any of these patients.

Of the patients with retention subjected to operation, 50 had been given at least 1 trial without the catheter but were unable to pass urine satisfactorily.

## Discussion

The finding of a high overall mortality rate (1.18%) and a particularly high rate in patients who had retention (3.3%) was unexpected and at first sight the difference in mortality rates between those catheterised pre-operatively and those not (3.18% vs 0.25%) might seem to suggest a fundamental fault in our management policy. However, closer study of the results indicated that those who fared worse were the patients for whom the traditional policy of "catheterise and keep in" had been followed, the mortality rate in this relatively small group being 12% compared with 1.8% in the "catheterise and send home" group. In addition, none of the patients who died had been subjected to catheter drainage for more than 3 weeks as against a mean duration of 7.84 weeks in those sent home with a catheter. The inference from these figures would be that prolonged catheter drainage is beneficial, but a more realistic deduction is that the patients operated on after relatively short periods of catheter drainage were those who were already in hospital because they were ill or were admitted to the urological ward because they had problems relating to their general health which made it inappropriate to send them home with a catheter.

There is no obvious reason for the increased risk of operation for the patients who had retention as against those who had not, a difference not apparent in our earlier series. Those with retention were significantly older and had larger resections but these factors alone are not sufficient to explain the difference. It would appear that the patients developed retention because of general debility and if this is so the hazards of operation must be increased.

It is clear that differential risks exist for prostatectomies. Wyatt *et al.* (1989) reported 4 deaths within 6 weeks of prostatectomy in a series of 90 patients aged over 80 years (4.4%). These authors did not relate the mortality rate to retention, but they did find a higher post-operative complication rate in patients who presented with retention, a risk also noted by Mebust *et al.* (1989). In our series there were 3 deaths within 6 weeks of TUR in 60 patients aged 80 years or more (5.0%). However, most of the patients who died were not demonstrably less fit than many of those who survived (the exception was patient 2 (Table 3): in retrospect it is clear that further pre-operative investigations should have been performed). It would be difficult to deprive so many patients of normal micturition. Perhaps stenting of the prostatic urethra (Williams *et al.*, 1989) will provide a safer alternative but at present its use is both expensive and unproven.

Our overall mortality rate of 1.18% compares favourably with the 1.4% (73 of 5190) reported by Graham (1977) but less so with the more recently reported 4 deaths in 2197 operations (0.18%) (Buckley *et al.*, 1989) and the 9 deaths in 3885 operations (0.23%) reported by Mebust *et al.* (1989). These results are difficult to reconcile with the 2.14% mortality rate in the first 1.5 months after operation reported in Medicare patients over the age of 65 with benign prostatic hypertrophy by Lubitz *et al.* (1985) and mortality rates ranging from 1.73 to 4.38% in the first 90 days reported by Roos *et al.* (1989), again in patients with benign hypertrophy. This latter study included results obtained from the Oxford Region (2171 patients between 1963 and 1978, mortality rate 4.39%), from Denmark (27,911 patients between 1977 and 1985, mortality rate 2.47%) and from Manitoba (8995 patients between 1972 and 1985, mortality rate 1.73%). These authors also demonstrated an increased operative risk for transurethral as opposed to open prostatectomy and suggested the possibility of a higher long-term mortality rate after transuretheral operations. However, they also stated "we cannot rule out potential confounding effects of unmeasured characteristics of patients" and every surgeon is aware of the virtually indefinable factors involved in assessing a patient's suitability for operation and the type of operation to be performed.

Despite these variations, there is little doubt that mortality rates for transurethral prostatectomy have fallen and in general it is a safe and reliable operation. This has resulted in the referral of patients who previously would have been regarded as unfit for operation. This places a special onus upon the urologist and if the mortality rate is to be further reduced, thorough pre-operative assessment and more careful post-operative management are required in those patients with retention. Alternatively, if an "all comers" policy is adopted, then these poor risk patients must be warned that a hazard exists.

Ideally, a patient with retention of urine would be catheterised, admitted to hospital, fully assessed and receive surgical treatment, all within the space of a day or two. In reality the process takes much longer. As indicated by Wyllie *et al.* (1988), the uneven flow of emergency admissions militates against the efficient use of hospital beds and even if beds are available, the need to add emergency cases will disrupt operating lists. Avoiding a large number of emergency admissions allows the use of a booking system which is attractive to patients and reduces the wastage of resources caused by the non-attendance of patients (Houghton and Broadribb, 1989). Few patients find the use of short-term catheters objectionable and most welcome any measure which will minimise their stay in hospital. The "Catheterise and send home" policy does not add to the risk of the operation and although some flexibility is required in order to accommodate the occasional patient who has problems with his catheter, we have no hesitation in continuing our present policy and recommending its use to other urological departments.

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# Interpretation of Biopsies of "Normal" Urothelium in Patients with Superficial Bladder Cancer

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Summary—In the course of a Medical Research Council trial of intravesical chemotherapy, biopsies were taken from apparently normal bladder urothelium near to newly diagnosed superficial bladder cancers in 417 patients. Differences were noted in the rates at which histological features were described in different centres. To gain more information about the reproducibility of the pathological findings, a group of 6 pathologists (5 from the UK and 1 from the USA), all having a special interest in urological pathology, were asked to examine a representative sample of 92 slides. They were then asked to re-examine 30 of them after an interval of at least 6 months. At first examination and at re-examination the slides were assessed using a standard proforma. However, the definitions of the categories were left unspecified for the pathologists to use their own criteria. The 5 UK pathologists then met to establish a consensus view of each slide.

The results indicated that: (1) The reporting of non-dysplastic changes varied so much between pathologists as to render it of little value to clinical practice. (2) There were wide variations between different pathologists in the reported incidence of dysplastic change. (3) On a second review the pathologists reproduced their own assessment on only 62% of occasions. (4) Even after discussion between pathologists there was no consensus on the diagnosis of mild as opposed to moderate dysplasia. Consensus was reached on all biopsies which showed either severe dysplasia or carcinoma *in situ*. (5) In adopting a policy of taking urothelial biopsies, urologists should be aware of the imprecision and lack of reproducibility in the interpretation of such biopsies. (6) Biopsies of cystoscopically normal urothelium may not be a useful guide in defining therapy.

It has been recognised for some time that in the presence of carcinoma *in situ* (CIS) in "normal" bladder biopsies the histological appearance of the primary tumour is not the only determinant of prognosis (Schade and Swinney, 1968). As a consequence, histological changes in apparently normal urothelium have formed an important part of the assessment of patients with bladder tumours (Cooper *et al.*, 1973; Schade and Swinney, 1973; Althausen *et al.*, 1976; Murphy *et al.*, 1979; Prout *et al.*, 1983; Wolf and Hojgaard, 1983).

Features described in cystoscopically normal urothelium include the presence of varying degrees of dysplasia extending to CIS (Murphy *et al.*, 1979), hyperplasia (Melicow, 1952; Wallace *et al.*, 1979; Heney *et al.*, 1983), atypia (Althausen *et al.*, 1976; Koss *et al.*, 1977; Wolf *et al.*, 1987) and inflammation (Althausen *et al.*, 1976; Wallace *et al.*, 1979).

In 1981 the Medical Research Council undertook a trial of intravesical chemotherapy in newly diagnosed superficial bladder cancer (MRC, 1985). Fifteen centres entered patients in the study. Biopsies of normal urothelium were taken from 2 sites in all patients, 1 adjacent to and 1 remote from the tumour. These biopsies were initially examined by the local pathologist. During the course of the study it became evident that there were wide differences in the rates at which various histological

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features were reported from different centres. For example, some local pathologists reported dysplasia in more than 35% of biopsies, whereas others did not report it at all. Further, a reference pathologist did not report dysplasia in any of the biopsies in his review of slides from 417 patients. Thus it seemed appropriate to look further at the biopsies and assess the reproducibility of the pathology of normal-looking urothelium.

## Materials and Methods

Between 1981 and 1984, biopsies of normal urothelium were taken from 417 patients entered into an MRC trial investigating the effect of instilling Thiotepa into the bladder at the time of primary resection of newly diagnosed superficial bladder tumours (MRC, 1985). Two biopsies were taken from each patient, 1 from within 2 cm of a tumour and a second at a site remote from all tumour. One hundred slides near to the tumour were selected randomly for study; 8 of these slides were subsequently found to be from patients ineligible for the randomised study referred to above because of muscle invasion and are therefore not considered further in this report.

Five pathologists from the UK (A, B, C, D and E), all with special interests in urological pathology, were invited to review the slides. In addition a pathologist (U) from the USA also reviewed the slides to enable a comparison between the UK and US pathology systems to be made.

In order to assess the variation between observers, the 92 slides were sent to each of the 6 pathologists in turn to be reported on without knowledge of the appearance of the primary tumour. No definition of any of the pathological characteristics was laid down, each pathologist interpreting the slides according to his usual practice. Each pathologist was asked first to classify the slides as either adequate or inadequate for assessment purposes. If the slide was considered adequate, he was then asked to report the presence or absence of the following features:

*(a) Non-dysplastic abnormalities.* Hyperplasia, metaplasia, inflammation, reactivity and atypia.

*(b) Dysplastic abnormalities.* For assessment of dysplasia the UK pathologists used the following grading system: absent, mild dysplasia, moderate dysplasia, severe dysplasia, CIS. Pathologist U used the system current in the USA: no CIS and CIS of Grade 1, 2 or 3.

To assess the variation within observers, 30 of the slides, selected to include about a 50% incidence of abnormalities, were reassessed by the same pathologists after an interval of at least 6 months. The slides were reviewed in such a way that the first assessment could not be traced by the pathologist at his second review.

The 5 UK pathologists then met to see if it were possible to reach a consensus view on the appearances of each of the 92 slides.

## Results

The details of the primary tumour diagnosis corresponding to the 92 biopsies of normal-looking urothelium are summarised in Table 1. The majority of tumours were stage pTA and Grade 1 or 2.

## Non-dysplastic Changes

### *Inter-pathologist variation*

The frequency with which the various non-dysplastic abnormalities were found by the individual pathologists is shown in Table 2.

**Table 1** Primary Tumour Diagnosis at the Time of Taking of Mucosal Biopsy of Cystoscopically Normal Urothelium Reviewed by Category, Multiplicity and Grade

| | *Tumour category* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *pTA* | | *pT1* | | *pTX* | | |
| *Grade* | *Single* | *Multiple* | *Single* | *Multiple* | *Single* | *Multiple* | *Total* |
| 1 | 40 | 12 | 0 | 0 | 3 | 0 | 55 |
| 2 | 9 | 4 | 4 | 2 | 3 | 0 | 22 |
| 3 | 0 | 0 | 6 | 6 | 3 | 0 | 15 |
| Total | 49 | 16 | 10 | 8 | 9 | 0 | 92 |

**Table 2** Number (%) of Non-dysplastic Abnormalities Reported by 6 Reviewing Pathologists in 92 Slides of Cystoscopically Normal Urothelium

| | *Pathologist* | | | | | |
|---|---|---|---|---|---|---|
| *Biopsy* | *A* | *B* | *C* | *D* | *E* | *U* |
| Inadequate | 7 | 3 | 6 | 2 | 9 | 1 |
| Adequate | 85 | 89 | 86 | 90 | 83 | 91 |
| No abnormality | 47 (55) | 9 (10) | 39 (42) | 77 (84) | 31 (34) | 30 (33) |
| Hyperplasia | 4 (5) | 10 (11) | 22 (22) | 1 (1) | 32 (39) | 7 (8) |
| Metaplasia | 3 (3) | 1 (1) | 5 (6) | 1 (1) | 6 (7) | 1 (1) |
| Inflammation | 32 (38) | 76 (88) | 27 (31) | 6 (7) | 20 (24) | 14 (15) |
| Reactivity | 0 (–) | 25 (28) | 14 (16) | 3 (3) | 6 (7) | 3 (3) |
| Atypia | 0 (–) | 0 (–) | 7 (8) | 5 (6) | 5 (6) | 52 (57) |

Percentages are expressed in terms of the number of slides considered to be adequate. There was a wide variation in the frequency with which different abnormalities were identified. Thus hyperplasia was found in 39% of cases by pathologist E but in only 1% by D. Inflammation was found in nearly all of the slides by pathologist B (88%), but only rarely by pathologist D (7%). Reactivity was reported in 28% of cases by pathologist B but less often by pathologists A, D or U (0, 3 and 3% respectively). Atypia was seen in over half (57%) of the slides by pathologist U but in less than 10% by the others.

*Intra-pathologist variation*

The level of agreement on a second look at those of the 30 slides in which the first assessment concluded that a particular abnormality was present is shown in Table 3. It can be seen that consistency across the 2 assessments was low for all of these characteristics, being particularly poor for hyperplasia and atypia.

**Table 3** Percentage Agreement in the Second Assessment given that the First Assessment of 30 Slides States the Condition is Present (UK pathologists only)

| *Abnormality* | *No classified as present at first assessment* | *% agreement at 2nd assessment across all pathologists* |
|---|---|---|
| Hyperplasia | 38 | 34 |
| Metaplasia | 10 | 60 |
| Inflammation | 68 | 70 |
| Reactivity | 17 | 65 |
| Atypia | 21 | 52 |

## Dysplasia

*Inter-pathologist variation*

The UK pathologists graded dysplastic changes as absent, mild, moderate, severe dysplasia, and CIS. However, Pathologist A did not distinguish the different grades of dysplasia and used a 3-point system of no dysplasia, dysplasia and CIS. Divisions between grades were set by the pathologists themselves and followed their own practice.

There was wide variation in the frequencies with which different dysplastic abnormalities were identified by the pathologists, as is indicated in Table 4. For example, pathologist C found mild or moderate dysplasia in 60% and severe dysplasia or CIS in 27% of slides compared to pathologist A, who found dysplasia in 6% and CIS in a further 7%.

*Intra-pathologist variation*

In those of the 30 slides considered to be adequate at both assessments, the pathologists replicated their first assessment precisely on 60% of occasions (Table 5).

However, disagreement was by only 1 grade, for example, between CIS and severe dysplasia or between mild and moderate dysplasia, in 30% of slides. Assessments differed by as much as 2 grades in the remaining 10%.

Frank CIS was diagnosed at first viewing on 14 occasions. Only 6 of these (43%) were reproduced on the second review. Of the remainder, 4 were subsequently reported as severe dysplasia, 2 as moderate dysplasia, 1 as mild dysplasia and 1 as non-dysplastic. This latter classification is thought to have been a transcription error. Combining CIS with severe dysplasia in a single joint category only improved the reproducibility to 46%.

The US pathologist (U) exhibited an 87% agreement with his first assessment and no disagreement was by more than 1 of his CIS grades.

**Table 4** Percentage of Dysplastic Abnormalities found by 6 Pathologists in 92 Slides of Apparently Normal Urothelium

| *UK classification of dysplasia* | *Pathologist* | | | | | *USA grade of CIS* | *U* |
|---|---|---|---|---|---|---|---|
| | *A* | *B* | *C* | *D* | *E* | | |
| Carcinoma *in situ* | 7 | 1 | 6 | 3 | 5 | | |
| Severe | | 6 | 21 | 1 | 1 | 3 | 4 |
| Moderate | 6 | 15 | 42 | 1 | 4 | 2 | 3 |
| Mild | | 13 | 18 | 11 | 10 | 1 | 26 |
| Total abnormal | 13 | 35 | 87 | 16 | 20 | Present | 33 |
| No dysplasia or CIS | 87 | 65 | 13 | 84 | 80 | Absent | 67 |

## Consensus

### *Non-dysplastic changes*

When the slides were reviewed at the consensus meeting it became clear that the non-dysplastic changes were too ill-defined to allow a consensus view. It was recognised that the differences between pathologists in the interpretation of non-dysplastic changes meant that reported changes were therefore unlikely to be of any assistance in assessing prognosis in patients with bladder cancer.

### *Dysplastic changes*

The 5 UK pathologists agreed that there were too many divisions for assessing dysplasia. The categories were thus broadened to combine mild with moderate dysplasia and severe dysplasia with CIS, as had been used by Pathologist A. The following uniform criteria were then agreed:

> Mild/moderate dysplasia—mild or moderate atypia of the component epithelial cells, with irregularity of shape or size and hyperchromicity of the nuclei. Mitoses may be present. There is some loss of surface orientated polarity.
>
> Severe dysplasia/CIS—irrespective of the number of layers, the urothelium is replaced by pleomorphic cells with hyperchromatic nuclei. Mitotic figures, which may be abnormal, are present and may be at any level. There is almost complete loss of stratification and polarity. There is no invasion. Much of the urothelium may have been shed.

**Table 5** Percentage Agreement of the Grading of Dysplasia between the First and Second Assessments of 30 Slides

| *Grade difference* | *UK Pathologist* | | | | | *Overall* |
|---|---|---|---|---|---|---|
| | *A** | *B* | *C* | *D* | *E* | |
| None | 93 | 54 | 32 | 57 | 69 | 60 |
| One | 7 | 28 | 47 | 36 | 27 | 30 |
| Two | | 18 | 14 | 4 | 4 | 10 |

*As A employed a 3-point system, his '1-grade' differences have been placed midway between the 1-grade and 2-grade differences on the 5-point scale.

The consensus classification of the 92 slides is summarised in Table 6. There was total consensus in the 4 cases from the clinically most important group of severe dysplasia/CIS.

The members of the panel were unable to agree—3 to 2 on 7 occasions and 4 to 1 on the other 3—about the presence or absence of mild/moderate dysplasia in 10 cases.

## Application of 3-Grade System to the First Assessments

If we apply the 3-grade system agreed at the consensus meeting to the first assessment by each of the UK pathologists working individually, agreement across all 5 pathologists was obtained on 9 of the 92 slides. Two of these were considered inadequate for review, 4 showed CIS/severe dysplasia, 1 a mild/moderate dysplastic change, 1 a non-

**Table 6** Number of Agreements and Disagreements at the Consensus Meeting of the 5 UK Pathologists

| *Consensus* | *Inadequate* | *Normal* | *Non-dysplastic* | *Mild/moderate dysplasia* | *Severe dysplasia/CIS* | *Total* |
|---|---|---|---|---|---|---|
| Yes | 10 | 16 | 50 | 0 | 4 | 80 |
| No | 1 | 0 | 1 | 10 | 0 | 12 |
| Total | 11 | 16 | 51 | 10 | 4 | 92 |
| Nature of disagreement | Non-dysplastic | — | Normal | Non-dysplastic | — | |

dysplastic change and 1 no abnormality. It is of interest to note that the 4 slides on which agreement was reached of severe dysplasia/CIS were the same 4 which were categorised as severe dysplasia/CIS at the consensus meeting.

## The USA and UK Grading Systems

A comparison with the results from the USA system was made by taking the UK consensus, or majority view when there was disagreement, to represent the UK position. The CIS Grades 1 and 2 in the US classification were not recognised as CIS by the UK pathologists, being either reported as a non-dysplastic condition (90%) or mild/moderate dysplasia (10%). The USA CIS Grade 3 always represented CIS in the UK classification.

## Prognosis

To consider the prognostic value of such biopsies we have used the UK consensus view. Of the 92 patients considered here, recurrences were noted in 47 patients (51%) during a median follow-up period of 3½ years. There was no obvious trend across the 3 groups for 2-year recurrence-free rates to be lower in patients with reported dysplasia and CIS (Table 7), although the numbers in this latter group are too small to make any definite statements.

Six of the 92 patients developed recurrent tumour which had progressed to muscle invasion during follow-up. Table 7 shows that 5 of these had G3 tumours initially. Progression to muscle invasion is rare (1/65) when the initial tumour was categorised as pTa, and was not seen in any of the 55 cases whose tumours were initially graded as G1. Invasion occurred once in 22 cases with initial G2 tumours. There was a slight tendency for progression to muscle invasion to be associated with the presence of dysplasia and CIS, although again the number of cases is too small to allow any conclusions to be reached.

## Discussion

The 92 biopsies studied were single biopsies taken from urothelium within 2 cm of the primary tumour. In every case the urothelium appeared normal endoscopically. Areas of local abnormality, for example, red, mossy or raised urothelium, were purposely avoided.

Non-dysplastic changes have been mentioned in several previous studies without any prognostic impact being attributed to them (Althausen *et al.*, 1976; Wallace *et al.*, 1979). It may be more difficult to be sure about the presence of dysplastic changes if non-dysplastic changes such as inflammation are also present. We conclude from this that non-dysplastic changes seem to be of little clinical relevance. It became clear during the course of the study that non-dysplastic changes such as inflam-

**Table 7** Recurrence-free Rates and Numbers Progressing to Muscle Invasion for the Histological Assessment of the Initial Tumour

| | | *No. of slides* | *2-year actuarial recurrence-free rates (%)* | *No. to muscle invasion* |
|---|---|---|---|---|
| Consensus Mucosal biopsy Assessment | Inadequate | 10 | 30 | 0 |
| | Normal | 17 | 62 | 0 |
| | Non-dysplastic | 58 | 60 | 3 |
| | Mild/moderate dysplasia | 3 | 33 | 1 |
| | Severe dysplasia or CIS | 4 | 50 | 2 |
| Multiplicity | Single | 68 | 63 | 3 |
| | Multiple | 24 | 32 | 3 |
| Grade | G1 | 55 | 64 | 0 |
| | G2 | 22 | 46 | 1 |
| | G3 | 15 | 38 | 5 |
| Category | pTa | 65 | 60 | 1 |
| | pT1 | 18 | 29 | 3 |
| | pTX | 9 | 60 | 0 |

mation or hyperplasia were ill-defined. It may be unwise for pathologists to refer to 'non-dysplastic' changes in reports of bladder biopsies as there is a possibility that they may then be allocated spurious clinical importance.

Unfortunately, the variability in interpretation by pathologists is also seen in dysplasia and CIS. Tables 4 and 5 emphasise the substantial variation in the frequency with which dysplastic changes were reported for the same slides, both by different pathologists at their initial examination—reported dysplasia ranged from 13 to 86% of slides—and by the same pathologist on re-examination of the same slide.

Although the 6 pathologists participating in the current study had agreed in advance on the broad categories of dysplasia and CIS which were to be reported, it was a matter of deliberate policy that no attempt was made to reach prior agreement on the changes which defined a particular category. The study makes it clear that different pathologists have differing views about the presence and severity of urothelial changes. It was possible to harmonise some but not all of their views during discussion. The variation was still present even when the original 5-point scale of grades of dysplasia was reduced to 3. Thus only a majority rather than consensus view could be taken on 12 of the 92 slides. Consensus agreement was not reached in any of the 10 cases (of these 12) in which at least 1 pathologist identified dysplasia. On the other hand, although this occurred in only 4 cases, a consensus was reached on the classification to severe dysplasia/CIS.

This study casts doubt on the prognostic importance of mucosal biopsies because of the lack of pathological reproducibility. It is not surprising, in view of the difficulty of making the diagnosis, that there was little association between the diagnosis of dysplasia or CIS and the tumour recurrence rate.

This is not the generally accepted position. Several authors (Althausen *et al.*, 1976; Heney *et al.*, 1983; Wolf and Hojgaard, 1983) have found that concomitant urothelial dysplasia predicts new neoplastic growth after transurethral resection. Wolf and Hojgaard (1983), for example, found recurrences in 13 of 15 patients with dysplasia but in only 7 of 22 when it was absent. On the other hand, Murphy *et al.* (1979) found evidence of a small effect only. It has not been established whether the effect of urothelial abnormality is associated with or independent of other easily measured factors, of which the most important are the number of tumours at presentation and the presence of tumours in the bladder 3 months after primary treatment (Parmar *et al.*, 1989).

The problem is complicated by differences in nomenclature. Wolf *et al.* (1987) noted that moderate to severe dysplasia in 1 classification (Koss *et al.*, 1977) corresponds to CIS grade II in another (Wolf *et al.*, 1987), while it is referred to as atypia or atypical hyperplasia in others (Soloway *et al.*, 1978; Wolf *et al.*, 1987).

A further factor which might influence the association between dysplasia and the recurrence rate is the number of biopsies taken to establish the presence of dysplasia. In the present study only 1 biopsy was studied. It seems unlikely that the difficulties of assessment observed in our study would be removed by studying a larger number of biopsies from each patient. Until the position is clarified it would seem unwise to base an aggressive management policy, generally employing intravesical chemotherapy, on the results of abnormal urothelial biopsies. Similarly, it is probably unwise to base entry of patients into a clinical trial on the results of biopsies of cystoscopically normal urothelium.

The difficulty which is evident among pathologists in agreeing on the diagnosis of dysplasia casts doubt on the published association between dysplasia and recurrence of bladder cancer. This doubt will remain until such time as pathologists agree on this diagnosis on the same biopsy.

The increasing accord which developed between the 5 UK pathologists at the consensus meeting gives ground for hope that a panel of pathologists could, given time, develop a consensus view. Even so it must be expected that until agreed criteria have been established for dysplasia and CIS of the bladder urothelium this view would most likely differ from the consensus view of other groups of pathologists, and particularly from that of a single pathologist working alone.

The variability in the reports obtained from different pathologists, and even from the same pathologists on different occasions, arises in part because there has been little discussion in the literature about the classification of dysplasia and CIS in the bladder.

Until a definition of the changes which can be seen in normal-looking urothelium can be agreed between pathologists and urologists and can be shown to be reproducible with an acceptable inter- and intra-pathologist variability, there will remain doubt concerning their relationship to recurrence rates and subsequent muscle invasion. If such reproducibility cannot be achieved, more objective means to evaluate urological pathology such as morphometry or DNA analysis may prove more useful.

It has been obvious to pathologists for a long time, but probably less obvious to urologists, that the precise interpretation of random mucosal biopsies is difficult. The present study indicates that the urologist must take these difficulties into account before adopting a policy of taking routine mucosal biopsies and when assessing the therapeutic consequences of reported dysplastic changes in the bladder.

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# Haemodynamic Evidence for Per-operative Cardiac Stress during Transurethral Prostatectomy

## Preliminary Communication

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Summary—Haemodynamic changes were measured during routine transurethral prostatectomy (TURP). The heart rate and stroke volume fell progressively over the first 30 min of surgery, resulting in a steady reduction in cardiac output. There was a significant increase in left ventricular afterload from commencement of the procedure. These findings demonstrate that haemodynamic responses, which are not detectable using conventional methods of monitoring, occur during TURP. Increased left ventricular afterload indicates increased myocardial work and oxygen demand which could result in myocardial ischaemia. This may contribute to the increased cardiovascular morbidity and mortality which have been reported to occur after TURP. The possible underlying mechanisms are discussed.

Transurethral prostatectomy is considered the optimum therapy for the relief of outflow tract obstruction (Chisholm, 1989) and has acquired an excellent reputation in terms of low hospital mortality, short in-patient stay and rapid return to normal life. Recent epidemiological work has, however, raised serious questions concerning the long-term mortality, especially from myocardial infarction, following this procedure (Wennburg *et al.*, 1987; Lancet, 1989; Roos *et al.*, 1989). A study of cardiospecific isoenzymes suggested that sub-clinical peri-operative myocardial damage does occur (Coppinger and Hudd, 1989). Survivors of myocardial infarction are more likely to have a further infarct and have an increased mortality rate. Per-operative myocardial damage could provide a link between TURP and increased long-term mortality.

If the cardiovascular system is adversely affected by TURP, then changes in cardiac performance should be seen per-operatively. There are, however, no data available on per-operative cardiovascular performance during routine TURP. Radioisotope dilution studies performed before and after TURP in an unselected group of 30 patients showed a fall in cardiac output of 17% (Mebust *et al.*, 1970). A study of 9 patients with intercurrent cardiac disease sufficient to merit a pulmonary artery catheter identified unpredictable haemodynamic responses, particularly an elevated pulmonary artery wedge pressure in 4 cases and marked changes in systemic vascular resistance in 7 cases (De Angelis *et al.*, 1982). While pulmonary artery catheterisation is inappropriate in a study of healthy patients undergoing routine TURP, oesophageal Doppler ultrasound is an equally accurate non-invasive method of following haemodynamic trends and responses. We therefore used this technique during TURP to look for evidence of per-operative cardiovascular embarrassment.

## Patients and Methods

Patients undergoing routine TURP were entered into the study. Prior approval was granted by the Middlesex Hospital Medical Ethical Committee and fully informed consent obtained from each

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patient. The cardiac risk index (CRI) was assessed using the Goldman classification (Goldman *et al.*, 1977). A standardised anaesthetic technique (Table 1), designed to cause minimal cardiovascular depression, was used by a single anaesthetist who concentrated on maintaining a stable blood pressure whilst unaware of the results of additional monitoring of blood flow and fluid balance.

TURP was performed with the patient in the Lloyd-Davies position, using intermittent irrigation with 1.5% glycine solution at room temperature delivered via a fast-flow set (Travenol, Thetford) from a reservoir set at 60 cm above the pubic symphysis. The surgical aim was to relieve prostatic obstruction by resection of sufficient tissue to achieve a clear and wide channel when viewed endoscopically rather than to remove the entire adenoma to the false capsule.

Blood loss was estimated from the total haemoglobin (Hb) loss, expressed as the product of the volume of irrigant collected and its Hb concentration in g/dl, measured by an OSM2 Hemoximeter (Radiometer, Copenhagen, Denmark). This figure was divided by the patient's pre-operative Hb level and multiplied by 100 to give the blood loss in ml.

Total fluid balance was determined gravimetrically using a system of transducers placed under the operating table, connected to a microcomputer programmed to give a continuous readout of the weight of the patient and operating table. The system was zeroed at the start of the operation and total per-operative weight gain measured at the end of the procedure. The system is accurate to ±50 g in a load of 275 kg. The irrigation fluid load is the difference between the expected (weight of fluid given intraveneously—blood loss—resected weight) and actual change in weight.

Haemodynamic data were obtained using a 5.1 MHz continuous wave oesophageal Doppler transducer connected to a spectral analyser system (Doptek, Chichester). The transducer was inserted orally after anaesthetic induction and positioned at approximately 35 cm from the incisors to focus on the midstream blood flow of the descending thoracic aorta as indicated by flow velocity waveforms with minimal spectral dispersion. Synchronous recordings of mean arterial blood pressure (MAP) and Doppler waveform parameters were made prior to instrumentation, then at 2 min into resection and at 10-min intervals thereafter until the end of the operation. The Doppler recordings were analysed post-operatively by an experienced operator using an integral software system.

Stroke distance (SD), the area under the flow velocity waveform, is a linear index of the left ventricular stroke volume. The integral software system averaged the area contained within 5 consecutive flow velocity waveforms and calculated the heart rate (HR) from the separation of the waveforms. Minute distance (MD), the product of SD and HR, is thus a linear index of cardiac output. An index of the systemic vascular resistance (ISVR) was calculated by dividing MAP by MD. This technique has been validated against thermodilution for measuring changes in cardiac output (Singer *et al.*, 1989; Singer, 1990).

Statistical analysis was performed using ANOVA (Statview II software).

## Results

Ten patients, 8 with benign prostatic hyperplasia and 2 with small foci of well differentiated adenocarcinoma, were entered into the study. Individual details, including the operator, age, cardiac risk index, weight resected, length of operation, haemorrhage, fluid load, maximum change observed and temperature change, are shown in Table 2.

**Table 1** Anaesthetic Protocol

| | |
|---|---|
| Premedication | Temazepam 10 mg |
| Induction | Thiopentone 4 mg/kg |
| Maintenance | Nitrous oxide 60% in oxygen, enflurane 0.5–1%<br>intermittent positive pressure ventilation<br>$CO_2$ 35±5 mmHg |
| Muscle relaxant | Vecuronium 0.1 mg/kg |
| Analgesia | Papaveretum 0.2 mg/kg on induction |
| Anaesthetic monitoring | |
| Blood pressure, electrocardiograph, oxygen saturation | Automatic sphygmomanometer and patient monitor 78354A (Hewlett-Packard Medical, Uxbridge) |
| End tidal carbon dioxide | Datex Normocap (SW Vickers, Sidcup) |
| Enflurane | Engstrom Emma (Gambro Engstrom AB, Sweden) |

**Table 2** Patients and Procedures

| | | | | | | | | Maximum change in: | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Operator* | *Age (years)* | *Cardiac risk index* | *Weight resected (g)* | *Histology* | *Duration of procedure (min)* | *Haemorrhage (ml)* | *Fluid load (ml)* | *HR (%)* | *SD (%)* | *MD (%)* | *ISVR (%)* | *Temp (°)* |
| R | 60 | 3 | 39 | BPH | 40 | 450 | 560 | −10 | −35 | −41 | +64 | NR |
| SR | 61 | 3 | 16 | BPH | 40 | 150 | 18 | −31 | −8 | −30 | +72 | NR |
| R | 85 | 12 | 13 | BPH | 30 | 240 | 0 | ±3 | −22 | −25 | +51 | NR |
| SR | 83 | 8 | 16 | BPH | 30 | 70 | 5100 | −6 | −40 | −43 | +43 | NR |
| SR | 64 | 0 | 20 | BPH | 30 | 110 | 180 | −19 | ±6 | −21 | +19 | NR |
| SR | 66 | 0 | 26 | BPH | 45 | 320 | 300 | +22 | −19 | −20 | +10 | −1·4 |
| SR | 64 | 0 | 28 | BPH | 55 | 170 | 200 | −19 | −18 | −32 | +48 | −0·9 |
| SR | 75 | 5 | 26 | CA | 40 | 140 | 270 | −9 | −13 | −21 | +42 | −0·4 |
| SR | 79 | 15 | 22 | CA | 50 | 320 | 1550 | −5 | −19 | −26 | +55 | −0·8 |
| C | 51 | 0 | 15 | BPH | 30 | 65 | 380 | −11 | −19 | −28 | +70 | −0·6 |
| Mean | 68 | 4·6 | 22 | | 40 | 203 | 856 | −8·5 | −19 | −29 | 47 | −0·82 |
| S.error | 3·5 | 1·7 | 2·5 | | 2·7 | 39 | 492 | 4·5 | 4·1 | 2·6 | 6·4 | 0·17 |

R = Registrar under supervision. SR = Senior Registrar. C = Consultant. BPH: Benign prostatic hyperplasia. CA = Carcinoma. HR = Heart rate. SD = Stroke distance. MD = Minute distance ISVR = Index of systemic vascular resistance.

The results of statistical analysis are shown in Table 3. While overall changes in MAP were not statistically significant, changes in HR, SD, MD and ISVR were significant. A steady fall in HR was seen which reached statistical significance at 20 min ($P<0.005$). A fall in SD was seen which became progressively more significant from 2 min ($P<0.05$) to 30 min ($P<0.001$). A fall in MD was seen which was significant from 2 min ($P<0.05$) and was progressive until 30 min ($P<0.001$). The ISVR showed an immediate rise by 2 min ($P<0.001$) which was sustained throughout the procedure.

These results are displayed as mean percentage changes from baseline in MAP, HR, SD, MD and ISVR in the Figure. There was a falling trend in both HR and SD. MD fell by 12% ±2.7 at 2 min and by 25% ±2.8 at the end of the operation; the maximum per-operative fall was 29% ±2.6. The ISVR rose by 32% ±8.2 at 2 min and remained elevated at this level throughout the remainder of the operation with a maximum per-operative rise of 47% ±6. The maximum per-operative fall in cardiac output was 29% ±2.6 and the maximum rise in ISVR was 47% ±2.6.

## Discussion

This study has shown that significant and unexpected haemodynamic responses occur during TURP. There was no relationship between the magnitude of haemodynamic change and either the operator, age, CRI, weight resected, length of operation, haemorrhage or irrigation fluid load. The age range and medical status of our subjects were representative of patients undergoing routine TURP. It is also significant that none of the resections were large or took longer than 55 min (average resection rate 0.5 g/min).

The oesophageal Doppler technique has been shown to be reliable and accurate in monitoring

**Table 3** ANOVA and Fisher PLSD Testing of the Effects of TURP Per-operatively and at the end of the Procedure

| *Measured variable* | *Overall ANOVA P value* | *2 min* | *10 min* | *20 min* | *30 min* | *End of procedure* |
|---|---|---|---|---|---|---|
| MAP | 0.13 | NS | NS | NS | NS | NS |
| HR | 0.0005 | NS | NS | <0.005 | <0.005 | <0.001 |
| SD | 0.0012 | <0.05 | <0.005 | <0.001 | <0.001 | <0.001 |
| MD | 0.0001 | <0.05 | <0.001 | <0.001 | <0.001 | <0.001 |
| ISVR | 0.0001 | <0.001 | <0.005 | <0.001 | <0.001 | <0.001 |

MAP = Mean artificial blood pressure. HR = Heart rate. SD = Stroke distance. MD = Minute distance. ISVR = Index of systemic vascular resistance.

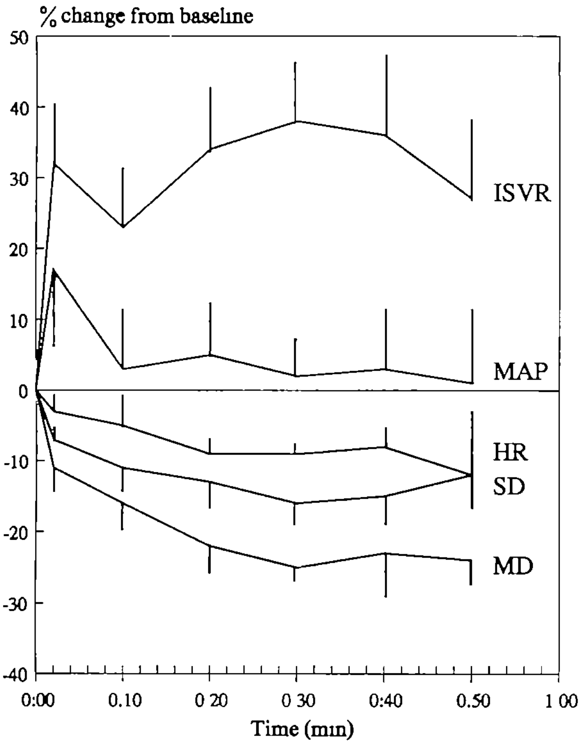

**Fig.** Haemodynamic changes during transurethral resection of the prostate.

haemodynamic changes over large variations in flow, pressure and temperature (Singer, 1990). Both the arm cuff of the automatic sphygmomanometer and the oesophageal Doppler probe remained in the same position throughout the operation. These non-invasive measurements are representative of per-operative haemodynamic trends.

A fall in cardiac output (CO) will occur in response to reduced preload, reduced myocardial contractility or increased afterload. Cardiovascular control mechanisms will result in a tachycardia if preload or contractility fall, whereas bradycardia and decreased stroke volume, as found in this study, would normally occur in response to a rise in afterload.

An increased afterload represents a stress to the myocardium because left ventricular work and myocardial oxygen demand will also rise. Inadequately perfused areas of myocardium could suffer ischaemic damage as a result. TURP is performed on elderly men who frequently have a compromised coronary circulation.

There are many factors which may contribute to haemodynamic responses during TURP. Irrigation fluid absorption, haemorrhage, anaesthetic agents (Ty Smith *et al.*, 1978; Morris *et al.*, 1983), glycine absorption and hyperammonaemia (Handler *et al.*, 1949; Guertzenstein and Silver, 1974; Hoekstra *et al.*, 1983; Hamilton Stewart and Barlow, 1989), sympathetic responses to surgery, the release of vasoactive substances into the circulation by resection (Von Euler, 1934, 1936; Verilli *et al.*, 1962; O'Donnell, 1983; Hahn, 1989) or responses to heat loss (Allen, 1973; Reuler, 1978; Rawstron and Walton, 1981; Carpenter, 1984; Chan and Mok, 1986) could all have a role.

The identification of adverse cardiovascular factors during TURP is of great clinical interest and supports the minimally invasive approach to outflow tract obstruction in the unfit patient (Lindner *et al.*, 1987; Chapple *et al.*, 1990; McLoughlin and Williams, 1990). The haemodynamic responses identified by this study require full investigation in a larger controlled study to evaluate their implications and aetiology.

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# Urethral Blood Circulation during Cardiopulmonary Bypass

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Summary—The haemodynamic changes induced by extracorporeal circulation (ECC) are thought to be important in the induction of urethral strictures in open heart surgery when indwelling latex catheters are used.

In the present study, 6 piglets were cannulated and connected to extracorporeal perfusion apparatus. Pump flows correlated with human ECC values with non-haemic prime were used. The mucosal and submucosal blood circulation in the urethra reduced by 66% during ECC ($P<0.05$). The brain and hepatic arterial flows increased. A significant reduction was seen in renal blood circulation.

The changes in the urethral blood circulation during ECC correlated with previous findings. The reduced wash out levels of chemicals leaching from the indwelling latex catheters as a result of reduced local blood circulation are the main trigger for the induction of urethral strictures during ECC and in other shock-like circulatory disturbances in the human body.

Urethral strictures induced by latex catheters have been reported to follow open heart surgery (Ruutu *et al.*, 1982; Sutherland *et al.*, 1983; Ferrie *et al.*, 1984; McEntee *et al.*, 1984; Nacey *et al.*, 1985). Latex urinary catheters have been shown to have toxic effects in both *in vivo* and *in vitro* biocompatibility tests (Graham *et al.*, 1983; Talja *et al.*, 1985; Nacey *et al.*, 1986).

Reduced local blood flow has been shown to increase the *in situ* cytotoxic effects induced by latex catheters in the urethra of experimental animals (Talja *et al.*, 1986b). This was originally suggested by Ruutu *et al.* (1982) and later emphasised by Sutherland *et al.* (1983) and by Abdel-Hakim *et al.* (1984).

We have already shown that the reduction in local urethral blood circulation induced by moderate haemorrhage in association with indwelling latex catheters resulted in marked urethral epithelial destruction and an inflammatory reaction (Talja *et al.*, 1986b).

The present study was undertaken to ascertain whether the haemodynamic changes that occur during extracorporeal circulation could cause similar effects in the urethral and periurethral tissue to those that follow slow haemorrhage; the model was the same as that used earlier by Talja *et al.* (1986b).

## Materials and Methods

Six male piglets weighing between 14.5 and 19.5 kg were used. Each animal served as its own control. The animals were anaesthetised with a combination of ketamine (Ketalar 10 mg/kg) and sodium pentobarbital (Mebumat 25 mg/kg) and intubated and ventilated with 40% $O_2$ in nitrous oxide. An arterial gas analysis was made at the beginning of each induction of anaesthesia to confirm the correct ventilation volumes.

A triple-lumen balloon tip thermodilution (Edwards Laboratory) Swan-Ganz catheter was inserted through the right vena jugularis externa. Cardiac output was measured as a mean of 3 well formed thermodilution curves using an Edwards

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cardiac output computer. For blood pressure measurements the aorta was cannulated through the left femoral artery. The tip of the catheter was kept just above the bifurcation of the iliac artery. The position was verified at the end of the experiment.

Extracorporeal circulation (ECC) was arranged with non-haemic prime (Ringer's solution) using a roller pump with continuous flow, a bubble oxygenator (Shiley −S70) and moderate hypothermia (30°C). The arterial cannula was connected to the ascending aorta. The venous cannulae were connected to the ascending and descending vena cava.

For pre-loading, Ringer's solution 75 ml/kg (mean) and sodium bicarbonate solution 8 ml/kg (mean) were used. In some animals the circulating blood volume had to be corrected with Haemaccel solution 30 ml/kg (mean) and Ringer's solution, so that the total use of Ringer's solution was 110 ± 7 ml/kg (mean). No vasoactive drugs were used.

Organ blood perfusion measurements were performed as described by Rudolf and Heyman (1967). Microspheres were injected via a catheter inserted into the right carotid artery with its tip in the left ventricle. The correct intraventricular position was checked by pressure measurement. For the collection of a reference sample, as well as for blood pressure measurement, we used the catheter inserted into the left femoral artery with its tip just above the iliac bifurcation. All catheters were heparinised.

Carbonised microspheres (NEN, New England Nuclear), $16.5 \pm 0.0$ µm, $16.5 \pm 0.1$ µm and $16.5 \pm 0.0$ µm in diameter labelled with $^{46}$Sc, $^{113}$Sn and $^{153}$Cd respectively, were suspended in 10% dextran containing 0.1% Tween 80. Immediately before injection the microspheres were evenly suspended by shaking for about 20s in a vortex shaker. A volume of 0.8 to 1.0 ml was injected slowly for over 10s. Each injection contained $3.5\text{–}4.5 \times 10^6$ microspheres. A reference sample (5 ml/min) was taken simultaneously with the injection of the microspheres.

The first injection containing microspheres labelled with $^{113}$Sn was given before the cannulation. The second injection contained microspheres labelled with $^{46}$Sc during the early extracorporeal circulation and the third injection contained microspheres labelled with $^{153}$Cd after 1 hour's ECC. The animals were sacrificed by exsanguination. The urethral mucosa together with the submucosa and other organ specimens were placed in plastic tubes. The tubes were weighed and the activity registered in an automatic gamma counter (Wallac). The organ blood flows were calculated with the help of the reference samples using a computerised program.

The paired *t* test was used to study the haemodynamic and local tissue flow changes. Significance was set at the level of $P < 0.05$.

## Results

*Haemodynamic changes.* The cardiac output (CO) was $3.0 \pm 0.37$ L/min before ECC. During ECC the pump output was recorded to be at an average level of 1 L/min. Despite this reduction the mean arterial blood pressure did not alter significantly. The change was from $87 \pm 1.4$ mmHg to $63 \pm 7.4$ mmHg during the early and $77 \pm 8.3$ mmHg during the late ECC. Blood cell volume fell from $0.28 \pm 0.02$ to $0.16 \pm 0.01$ and finally to $0.15 \pm 0.01$ due to non-haemic priming (Table 1).

**Table 1** Systemic Haemodynamic Changes Induced by Extracorporeal Circulation (mean ± SEM, n = 6)

| | |
|---|---|
| Cardiac output (L/min) | |
| Pre-CPB | 3.0 ± 0.5 |
| CPB, at the start | 1.3 ± 0 08 |
| CPB, at the end | 1 0 ± 0.03 |
| Mean blood pressure (mmHg) | |
| Pre-CPB | 87 ± 1.4 |
| CPB, at the start | 63 ± 7.4 |
| CPB, at the end | 77 ± 8.3 |
| Haematocrit | |
| Pre-CPB | 0.28 ± 0.02 |
| CPB, at the start | 0.16 ± 0.01 |
| CPB, at the end | 0.15 ± 0 01 |

CPB = cardiopulmonary bypass

*Changes in tissue perfusion.* Blood flow in the urethral mucosa decreased from $7.2 \pm 1.9$ to $2.2 \pm 0.6$ ml/100 g/min; this was statistically significant ($P < 0.05$). The variation between individual animals was great, with decreases between 21 and 88% being seen. The blood flow to the kidneys was symmetric and the reduction was significant ($P < 0.05$). Blood flow in the liver and brain increased during ECC, the latter only in the early phase. Muscle and skin blood circulation was not significantly reduced (Table 2).

## Discussion

The epidemics of urethral strictures in open heart surgery patients in the early 1980s (Ruutu *et al.*, 1982; Smith and Neligan, 1982; Sutherland *et al.*, 1982; Walsh, 1982; Wesley-James, 1982) have been

**Table 2** Blood Circulation Changes in Various Organs after 1 Hour's ECC (ml/100 g/min, mean ± SEM, n = 6)

| | *Pre-CPB* | *Post-CPB* |
|---|---|---|
| Urethra | 7.20 ± 1.9 | 2.18 ± 0 6 $P<0.05$ |
| Kidney | 239 ± 18 | 114 ± 18 $P<0.05$ |
| Liver, arterial | 41 ± 6 | 71 ± 18 NS |
| Brain | 32 ± 3 | 37 ± 16 NS |
| Muscle | 5.1 ± 0.8 | 3.2 ± 1 2 NS |
| Skin | 1 8 ± 0.5 | 0 7 ± 0.2 NS |

CPB = cardiopulmonary bypass.

intensively investigated. Our earlier studies revealed considerable variation in the tissue biocompatibility properties of latex catheters and many of these catheters were shown to be highly tissue-toxic (Talja *et al.*, 1985). The most severe urethral side effects (tight urethral strictures usually involving the whole urethra) occurred in the open heart surgery patients. To establish whether the circulatory changes in these patients during ECC affected the pathogenesis of the strictures, an experimental study was carried out in which slow haemorrhage was induced in piglets to mimic the circulatory changes caused by ECC. The blood circulation in the urethral mucosa was reduced by 75% when the haemorrhage volume was 35% (Talja *et al.*, 1986a). At the same time the epithelial damage induced by latex catheters of different tissue toxicities increased markedly. Destruction of the whole epithelium was observed in association with the worst tolerated catheters (Talja *et al.*, 1986b). In the normovolaemic animals the epithelial changes were minimal.

In this study, the blood circulation changes in the previous haemorrhage model were compared with those seen in the ECC model. It is known that extracorporeal circulation has multiple effects on regional haemodynamics. Blood pressure falls suddenly during cardiopulmonary bypass (CPB), rising later as a result of vasoconstriction (Kirklin *et al.*, 1983). Although peripheral circulation is augmented by haemodilution, increasing blood viscosity by hypothermia, reduction of blood pressure and endocrine responses to ECC result in a reduction of peripheral circulation as a net effect (Vanhoute and Shephard, 1970).

In the present study the pump levels used were only one-third of the pre-perfusion cardiac output level. Levels even higher than pre-CPB are used to preserve the peripheral blood circulation (Niinikoski *et al.*, 1981). However, the level of perfusion flow was in accordance with that used by the present perfusion team before and during the epidemics of urethral strictures discovered earlier (Ruutu *et al.*, 1984). The peripheral blood flow values during the early CPB were 80 ml/kg/min (= n. 2.5 L/min/m$^2$, mean) and during the late CPB were 60 ml/kg/min (= n. 2.0 L/min/m$^2$, mean). Because the corresponding temperatures were 32 and 28°C, these flow values were acceptable (Kirklin *et al.*, 1983).

With the present pump levels, the reduction in blood pressure was 38% in the early CPB and 24% at the end of ECC, which correlates with the pre-CPB level. The reduction in blood pressure in our earlier haemorrhage model was the same (25%) (Talja *et al.*, 1986a). The correlation in the systemic haemodynamic changes between the present and our earlier study is obvious. Sakautchi *et al.* (1976) reported a similar correlation. In both of these studies the circulatory changes were based on the same humoral reflexes to maintain the haemodynamic equilibrium.

The dependence of urethral blood flow on total systemic flow was in accordance with that found in the earlier haemorrhage model. A 67% reduction in systemic flow reduced urethral blood flow by 66% during CPB, and a 35% reduction in systemic flow reduced urethral blood flow by 74% during haemorrhage (Talja *et al.*, 1986a). The systemic flow values during CPB and normal heart pump flow cannot be directly correlated because of the special properties of the pump flow.

The reductions observed in the kidney, muscle and skin blood flow during CPB were also compatible with flow dependency and were analogous to the results of the haemorrhagic shock models of Neutze *et al.* (1968), Kaihara *et al.* (1969) and Pang *et al.* (1986). This dependency is in sharp contrast to the behaviour of autoregulated vascular beds such as the brain. Govier *et al.* (1984) also reported that cerebral flow was unchanged in man when the systemic flow was reduced from 2.0 to 1.0 L/min/m$^2$ during CPB.

The results of the present study support the hypothesis that reduced urethral blood flow during ECC exacerbates the harmful effects of poor quality latex catheters. The mechanism suggested is that the toxic chemicals leaching from the catheters reach high concentrations *in situ*. The hypoperfused epithelium may also be particularly sensitive to chemical injury and may react by extensive inflammation and consequent scarring.

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# Optical Urethrotomy under Local Urethral Anaesthesia

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Summary—A series of 46 patients underwent 76 optical urethrotomies under local urethral anaesthesia in the out-patient clinic; in 70% of patients the strictures were controlled by local anaesthetic urethrotomy alone; 61% felt either no pain or mild pain during the procedure; 72% expressed a preference for local anaesthesia should the procedure have to be repeated and 82% were happy with the result of their treatment.

Optical urethrotomy under local urethral anaesthesia produces results comparable to those reported by others using general anaesthesia. If large numbers of patients are to be treated, possibly repeatedly, then out-patient urethrotomy may result in more efficient use of resources.

Since its introduction, optical urethrotomy has become widely accepted as the treatment of choice for urethral strictures. Used alone, it can control up to 80% of these strictures (Matouschek, 1978; Gaches *et al.*, 1979; Holm-Nielsen *et al.*, 1984).

The procedure is usually performed on an in-patient basis under general anaesthesia with a variable period of post-operative catheterisation (Lipsky and Hubmer, 1977; Smith *et al.*, 1978). Since urethral strictures are common and many require repeated treatment, out-patient urethrotomy could result in more efficient use of resources.

Several reports have discussed the question of optical urethrotomy using local anaesthesia (Matouschek, 1978; Gaches *et al.*, 1979; Barkin *et al.*, 1983; Stone *et al.*, 1983) but there has been no formal evaluation of its acceptance by patients and its results.

We present a retrospective analysis of optical urethrotomy under local urethral anaesthesia together with the results of a postal questionnaire.

## Patients and Methods

The series comprised 76 urethrotomies under local urethral anaesthesia on 46 male patients between June 1986 and April 1989 (34 months). The patients' median age was 67 years (range 25–84); 25% had had symptoms for less than 1 year and the mean duration of symptoms was 3 years (range 3 months–32 years). Previous urethral instrumentation was the leading cause of stricture (Table 1) with over 50% occurring in the bulbar urethra (Fig. 1). Of 29 patients with recurrent strictures, 25 had had a previous urethrotomy under general anaesthesia and 4 a urethral dilatation.

**Table 1** Aetiology of Strictures

| *Type* | *No (%)* |
|---|---|
| Inflammatory | 5 (13) |
| Traumatic | 3 (8) |
| Instrument/traumatic | 20 (50) |
| Congenital | 1 (3) |
| Undetermined | 11 (28) |

In all cases the technique used was that routinely employed under general anaesthesia except that 20 ml of 2% lignocaine jelly were introduced into the urethra 3 to 5 min prior to the instrumentation to provide anaesthesia. Prophylactic antibiotics were not used and the patients received neither sedation nor analgesia since they were required to leave the clinic immediately after the procedure. They were not catheterised post-operatively and were advised to drink plenty of fluids until the

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Based on a Poster Demonstration at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

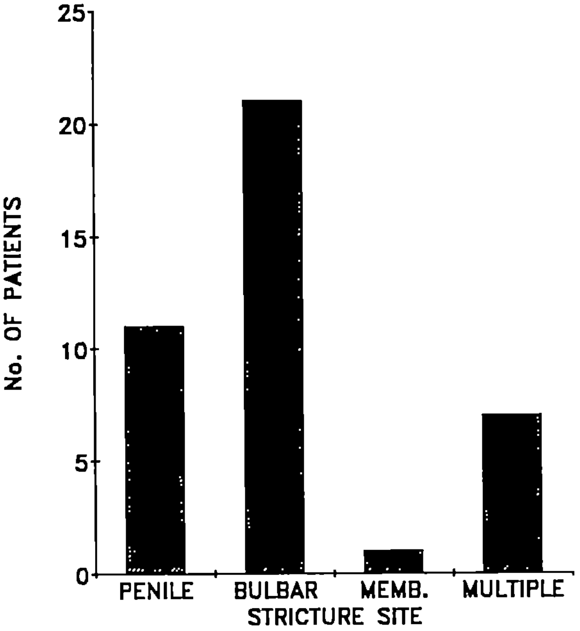

**Fig. 1** Site of stricture as determined by urethroscopy; over 50% of the strictures were in the bulbar urethra.

inevitable urethral bleeding, which they were warned to expect, had stopped.

Uncomplicated new patients were discharged directly back to the care of their family doctor with instructions to re-attend should their symptoms recur. The remainder were reassessed after a 3-month interval. Repeat urethrotomies were performed as required according to the patients' subjective assessment of their flow rate but post-operative urine flow rates were not formally measured on all patients.

The patients were contacted by postal questionnaire 3 months after the end of the study period. This assessed pain by means of a visual analogue scale (Fig. 2) and pre- and post-treatment urine flow (Fig. 3). We enquired whether they would prefer either a general or a local anaesthetic should the procedure need to be repeated and whether or not they were happy with the result of their treatment.

No pain__________×______________________________Worst pain
imaginable

**Fig. 2** Visual analogue scale used to assess pain. Patients were asked to mark a blank 10-cm line according to their experience of pain. The pain was scored by measuring, in centimetres, the distance of the patient's mark from the left end of the line. In this example mild pain (score = 2) was experienced.

Before At present
____________________ Excellent ____________________
____________________Very Good____________________
____________________ Good ____________________
____________________ Poor ____________________
____________________ Very poor ____________________

**Fig. 3** Method of assessing pre- and post-urethrotomy flow rates Patients were asked to tick the appropriate spaces. The subjective result of the urethrotomy was then scored by counting the number of lines by which the mark had moved.

## Results

Completed questionnaires were not available for 6 of the 46 patients; 3 had died, (2 with carcinoma of the prostate and 1 with invasive bladder cancer) and 3 patients failed to return the questionnaire. Thus 40 questionnaires were suitable for complete analysis.

A total of 24 patients (60%) experienced no pain or only mild pain (Fig. 4) and 5 patients (13%) experienced severe pain. Three procedures had to be abandoned—2 due to pain and the third as a result of bleeding. Seven urethrotomies (9%) resulted in complications (Table 2). Admission to hospital was required following 4 urethrotomies (6%), 3 because of bleeding and 1 because of acute

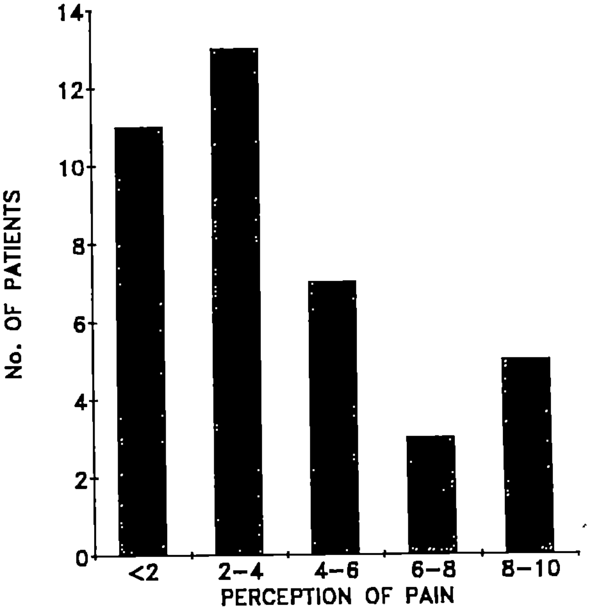

**Fig. 4** Patients' perception of pain during urethrotomy as deduced from the visual analogue scale, 62% had either no pain or just a progression to mild pain.

Table 2 Complications

| *Complications* | *No. (%)* |
|---|---|
| Bleeding | 3 (4) |
| Infection | 1 (1) |
| Retention | 2 (3) |
| False passage | 1 (1) |

retention. Significant bleeding was defined as that requiring catheterisation and admission. The second patient who developed acute retention was catheterised and discharged home. He passed urine freely on removal of the catheter a few days later.

During a median period of 15 months (range 3–34) following their first urethrotomy, 28 patients (70%) required no treatment other than optical urethrotomy under local anaesthesia; 23 patients (58%) required only 1 treatment. Twelve patients (30%) were defined as treatment failures because they required an alternative form of treatment to control their stricture. Intermittent self-dilatation with low-friction catheters was used in 10 patients (25%) with 1 patient requiring a urethrotomy under general anaesthesia and the other a urethroplasty.

When asked about their preference for either general or local anaesthesia for subsequent procedures, 29 patients (73%) expressed a preference for local anaesthesia; 33 patients (83%) were satisfied with the result of their procedure and their subjective assessment of success is shown in Figure 5; 23 patients (58%) reported an improvement of 2 or more points on the scale.

## Discussion

Optical urethrotomy is usually performed as an in-patient procedure under general or spinal anaesthesia and patients are routinely catheterised post-operatively (Lipsky and Hubmer, 1977; Smith *et al.*, 1978).

Smith *et al.* (1983), in contrast to their earlier report (Smith *et al.*, 1978), demonstrated that varying duration or lack of urethral catheterisation had no effect upon the outcome and that catheters were required only to drain excessive post-operative bleeding. Other studies have failed to show that long-term catheterisation is any better than short-term catheterisation (Johnston *et al.*, 1980; Holm-Nielsen *et al.*, 1984). In view of these findings, our patients were not routinely catheterised.

We have shown that satisfactory urethral anaesthesia can be achieved in the majority of patients by using 2% lignocaine jelly. The procedure has a low complication rate, although minor complications (such as infection) may have been dealt with by the family doctors without our knowledge.

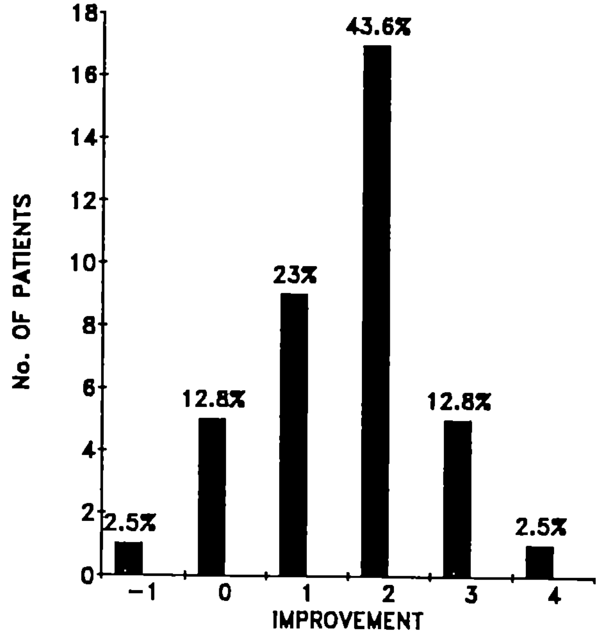

Fig. 5 Patients' subjective assessment of success of treatment by comparing pre- and post-operative flow (see Fig 3).

The overall success rate of 70% compares favourably with that of 75 to 80% reported by others (Matouschek, 1978; Gaches *et al.*, 1979; Smith *et al.*, 1983; Holm-Nielsen *et al.*, 1984). Our period of follow-up is comparable to that of several other series (Gaches *et al.*, 1979; Johnston *et al.*, 1980; Desmond *et al.*, 1981; Boccon Gibod and Le Portz, 1982; Holm-Nielsen *et al.*, 1984) and it is reported that the majority of stricture recurrences following optical urethrotomy develop within 1 year (Matouschek, 1978; Desmond *et al.*, 1981; Stone *et al.*, 1983; Pain and Collier, 1984).

We did not measure post-operative urinary flow rates since the majority of our patients were discharged directly back to the care of their family doctor. Whilst a post-operative flow rate measurement must be regarded as the most accurate method of assessing success, Johnston *et al.* (1980) demonstrated a good correlation between flow rates subjectively assessed and objectively measured before and after urethrotomy.

Whilst the exact success rate reported for any series will depend upon the criteria used to define success and the period of follow-up, we feel that the results of the present study were not significantly affected by our methods and indeed they compare favourably with the 50 to 60% success rate reported by others (Desmond *et al.*, 1981; Boccon Gibod and Le Portz, 1982).

This was a selected group of patients. Those with complicated strictures or concurrent pathology were admitted for urethrotomy under general anaesthesia. The proportion selected for out-patient urethrotomy has increased over the course of the study as we found that it was acceptable to patients and that it produced good results.

Optical urethrotomy under local anaesthesia is a safe, effective and well tolerated procedure which will produce significant savings in the cost of treating patients with urethral strictures.

## Acknowledgements

We wish to thank Mr M. A. Hughes for allowing us to report upon his patients and also to thank the Senior Registrars of the Department of Urology who carried out some of the urethrotomies reported on here.

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# Abstracts of the Proceedings of the Urological Society of Australasia, 43rd Annual Scientific Meeting, Darwin, Australia, 1990

*President:* P. O. Maher
*Secretary:* D. Golovsky
*Editor:* R. J. Millard

The 43rd Annual General Meeting of the Urological Society of Australasia was held at the Beaufort Hotel, Darwin, Australia from 27 May to 3 June 1990. The meeting was organised by Mr Peter Maher, President of the Society, and a committee from Sydney. Principal guests of the meeting were Mr R. Hall from Newcastle upon Tyne, England, Professor R. Hartung of the Technische Universität, Munich, Germany, and Professor M. Resnick from Case Western University, Cleveland, USA.

The programme featured keynote presentations from principal guests on the topics of laser therapy, stones, bladder outlet obstruction, cancer and paediatrics. The Harry Harris Oration was delivered by Professor Alan Powell, Dean of Arts, North Territory University, on the subject, "The Australian Aborigines; Past, Present, and the Future".

The Keith Kirkland prize for the best paper presented by a trainee was awarded to Dr M. Frydenberg for his paper on Growth Factor receptors in prostatic disease.

The Alban Gee prize for the best poster went to Mr A. Low for his presentation on the Brindley Sacral Root Stimulator.

The 44th ASM of the Society will be held at the Sheraton Mirage Hotel, Gold Coast, Queensland, between 14 and 19 April 1991.

## Lasers in Urology

### Lasers in Urology

R. Hall
Freeman Hospital, Newcastle upon Tyne, UK

Lasers were invented 30 years ago and although they have found an important role in gynaecology, ENT, ophthalmology and upper GI surgery, their usefulness in urology is still to be defined. The effect of different lasers (and their role in urology) depends upon the wavelength of the light they emit.

The carbon dioxide laser has been evaluated extensively in urology and its only worthwhile application is for the vaporisation of carcinoma *in situ* of the glans penis. Its lack of haemostasis and its reluctance to pass along optical fibres are major limitations to its use.

Nd: YAG lasers are used mainly for their thermal coagulation of tumours of the bladder, penis and prostate. This laser is transmitted by optical fibres and is ideal for combination with the flexible cystoscope for the fulguration of bladder tumours up to 1 cm with only topical anaesthesia. Several authors have claimed that laser treatment is followed by reduced local recurrence of transitional cell tumours compared with diathermy transurethral resection, but this has not been proved by adequate randomised trials. Such a trial is being organised by the EORTC.

However, small tumours can be treated by diathermy coagulation without anaesthesia in similar circumstances. For larger superficial tumours the Nd: YAG laser is very slow and its thermal coagulation precludes proper histological assessment of tumour invasion. Conventional TUR is preferable.

Invasive penile carcinoma of limited extension can be treated successfully with Nd:YAG, preserving function by avoiding amputation or radiotherapy.

Biesland and Sander have used this laser to achieve local control of stage A and B prostate cancer by applying it to the prostate capsule after a thorough prostatic resection. Their single-institution results are encouraging and appear comparable to those of radical prostatectomy but patient numbers are small, median follow-up <5 years, and further trial is necessary.

The light produced by argon, copper vapour and some dye lasers is absorbed preferentially by haematoporphyrin and related pigments. This phenomenon has been developed for the photodynamic treatment of carcinoma *in situ* and multiple Ta/T1 tumours of the bladder. Unfortunately the pigments cause general photosensitisation for several weeks, technical problems of instrumentation have not been resolved and the clinical potential of this form of laser treatment has yet to be realised.

The latest urological application of lasers has been the lasertripsy of ureteric and renal pelvic calculi using pulsed dye lasers, delivered by a fine optical fibre via a rigid or flexible ureteroscope. The method is undoubtedly effective and only future comparisons with ESWL and the latest electrohydraulic probes will prove if the expense of lasertripsy is justified.

## Photodynamic Therapy in the Treatment of Experimental Urinary Bladder Tumour

W. Han, A. Kaye, J. Hill, S. Stylli and G. J. Clunie
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Photodynamic therapy (PDT) is an experimental cancer treatment that uses light of selected wavelength to induce the preferential destruction of previously sensitised tumour cells. This treatment is gaining widespread use in the management of a variety of human tumours including bladder cancer. In this study the uptake of the photosensitiser haematoporphyrin derivative (HpD) into human bladder tumours (BD-17) implanted into athymic nude mice was determined. In addition, the photodynamic effect following exposure to the light of appropriate wavelength was determined on this tumour model, and on the rat bladder tumour cell line (NBT-II) *in vitro*. The maximal uptake of HpD into the implanted tumour was observed 24 h following a dose of 20 mg HpD/kg body weight (i.p.). The *in vitro* tumour cell phototoxicity was measured by colony survival, as dependent on light and HpD dosage.

Exposure of the bladder tumour cells to white light for 3 min in the presence of 2.5 μg HpD/ml medium resulted in 0% colony survival. Control studies resulted in 85% colony survival of sensitised cells in the absence of light, and 100% survival of cells exposed to light in the absence of HpD.

Preliminary studies of PDT treatment on the implanted tumours sensitised by i.p. injection of 20 mg HpD/kg body weight 24 h prior to 200–400 J/cm$^2$ of 628 nm laser light showed that tumour phototoxicity was dependent on laser dosage and initial size of the tumour. The best result was gained when tumours of 3–4 mm diameter were treated with laser light of 400 J/cm$^2$. Following treatment of 6 mice at these HpD and light doses, 3 were tumour-free 2 weeks after PDT. In contrast, in control mice treated with laser alone, HpD alone or untreated mice, no effect on tumour growth was observed.

## Re-establishing Continuity of the Genitourinary and Alimentary Tracts Using Combination Laser Tissue Fusion and Indwelling Biosoluble Stents

A. Costello and D. E. Johnson
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Low-level laser energy has been used either alone or adjunctively to re-establish the integrity of a number of smooth-muscle organs (fallopian tubes, arteries, bowel, vas deferens, ureter and urethra). However, difficulties in maintaining accurate seromuscular apposition of tubular organs for precise placement of the laser beam have hampered both laboratory and clinical investigations. Using biocompatible water-soluble, intraluminal stents, we have satisfactorily constructed totally sutureless bowel anastomoses and laser-assisted vasovasostomies and ureteroureterostomies in animal models.

Sutureless end-to-end intestinal anastomoses were successfully constructed in 20 rabbits by applying 5 watts of 1.06 u Nd:YAG energy through a hand-held 600 u gas-cooled non-contact optical fibre for periods ranging from 46 to 92 s. Integrity, degree of tissue reaction and bursting pressures of the anastomoses were compared with those of standard sutured anastomoses.

The results were equivalent at 1–3 days, but at 7 and 14 days the laser-fused anastomoses showed less inflammatory reaction, better healing and greater bursting pressures.

Similar results were achieved using smaller stents and 2–3 watts of power from $CO_2$ lasers to perform vasovasostomies in rabbits and ureteroureterostomy in a dog. Because these latter techniques markedly reduce the need for placement of microsurgical sutures, they have simplified and shortened the operative procedures.

We conclude that using lasers as reconstructive rather than ablative instruments offers promising alternatives for this surgical technology.

## Laser Treatment of Human Papillomavirus Lesions in 150 Males

C. Rowling
Perth, Western Australia

Clinical inspection alone is unreliable for wart virus lesions on the penis. A review of the first 150 male patients was undertaken. Most of the patients (85%) were contacts of women with documented cervical papillomavirus changes (Papanicolaou smear/biopsy). Mean age was 30.8 years, 25% had undergone previous treatment for genital warts and 3% had had multiple modes of previous treatment; 78% were circumcised.

Examination using 10% acetic acid as a disclosing agent and immediate examination with a colposcope was performed. If aceto white dots or lesions suggestive of HPV infection were found these were recorded and a biopsy performed. If the biopsies were negative and a high index of suspicion remained, repeat biopsy was performed. The major treatment was $CO_2$ laser and close follow-up. Of patients with positive biopsies 25% failed to attend for treatment after biopsy and a further 8% defaulted follow-up. Aceto white lesions required biopsy in 85% and 53% were positive for human papillomavirus-induced changes. Of 10% who underwent repeat biopsy only 1 converted to a positive category. Of those men presenting with what was thought to be clinical wart lesions 55% had demonstrable HPV and a slightly smaller number with colposcopically apparent sub-clinical aceto white dots had demonstrable wart virus on biopsy. There was no significant difference between these 2 groups for rate of positive biopsy. However, with both clinical warts and sub-clinical aceto white dots the diagnostic yield was 83% ($P$ 0.01, $\chi^2$).

## Experimental and First Clinical Results with the Alexandrite Laser—Lithotriptor

K. Miller, H. M. Weber, J. Ruschott and R. E. Hartmann
Ulm, Germany

We have carried out *in vitro* lithotripsy trials in order to evaluate the efficacy of flash-lamp pumped, Q-switched Alexandrite lasers (Dornier Medical Systems) for lithotripsy. The Alexandrite emits a wavelength of 750 nm; a pulse energy between 20 and 70 mJ/pulse is available. In association with a pulse duration in the hundred nanosecond range this system allows the use of 200 μm quartz fibres without the hazard of destroying the fibre tip during lithotripsy.

For a first assessment a stone model, recently developed for ESWL, was modified for the purposes of laser lithotripsy: a 1.2 cm plaster ball is positioned in a rigid net (pore size 2 mm) which is immersed in a waterbath. The time required to break the stone into fragments <2 mm can be used as a measure of the efficacy of the lithotripsy system. The time required to empty the net completely was about 8 min and thus parallels the duration obtained with a Q-switched Nd:YAG laser.

Further studies were then carried out in a similar setting using human stone material gained in the course of percutaneous or open operations: 4 ca-oxalate monohydrate stones (obtained from 4 patients, 2 of whom had undergone unsuccessful ESWL), 2 cystine stones and 2 ca-phosphate/struvite stones were tested. Stone size ranged from 7 to 20 mm (measured at largest diameter).

Stone disintegration was successful in all but 1 of the ca-oxalate monohydrate stones (large stone with smooth surface). The time required for fragmentation ranged from 5 to 12 min (depending on stone size and composition), with a 10 Hz repetition rate of the laser. Thus this system holds promise for a further evaluation in a clinical setting: a prototype for clinical trials will be available from October 1989.

## The Pulsed Dye Laser for Urinary Calculi in 600 Patients

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The pulsed dye laser has been used clinically at this institution since October 1985. Initially it was used with conventional ureteroscopes of 11.5 F. With the development of a miniaturised 7.2 F ureteroscope complications have been reduced. Actively-deflectible ureteroscopes (9.5 F) enable access to calculi in almost all clinical situations. Fragmentation by laser is safer than by electrohydraulic probes and generates less heat than ultrasonic probes.

The first 100 patients were treated using an 11.5 F ureteroscope alone. We now use a miniaturised 7.2 F ureteroscope (the MiniScope) and then only if necessary pass a flexible ureteroscope. Results are quoted for the first 100 and latest 100 patients respectively. Access to the stone was successful in 77%, increasing to 99%. The average time required to reach the stone was 50 min, reducing to 6 min.

Ureteric perforation fell from 7 to 0%. The requirement for a double pigtail stent for mild ureteric trauma fell from 45 to 6%. Needle nephrostomy requirement fell from 7 to 0%. Ureteric stricture (never at the site of the stone fragmentation) fell from 3 to 0%.

With increasing success we have expanded the role of laser lithotripsy to become the first-line management for upper third stones. The incidence of upper third calculi was 20% in the first 100 patients and has risen to 56%. We have used the laser via the MiniScope in the renal pelvis in 11 patients and via the flexible ureteroscope in the calices in 3 (with 1 failed access in a pelvic kidney). The flexible ureteroscope has been used for antegrade ureteroscopy (via a percutaneous track through the kidney and into the ureter) whenever retrograde ureteroscopy was impossible, as in stones in the ureter of a transplant kidney or after uretero-sigmoidostomies. Open surgery for a ureteric calculus alone has not been required for the last 3 years.

## Neodymium: YAG Laser Lithotripsy of Ureteric Calculi

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After testing a high intensity nanosecond pulsed neodymium: YAG (Nd:YAG) laser for its biological effect in animal studies, we found that the YAG laser did not cause any serious damage and in June 1987 we began to use it in the treatment of patients.

The laser energy of a neodymium: YAG laser with an 8 ns pulse at up to 50 Hz was coupled into a flexible 600 resp. 400 µm quartz fibre. Laser-induced breakdown was created with 35 to 50 mJ at the fibre tip, resulting in a shock wave that disintegrated the calculus into tiny fragments. A 9 or 11 F rigid ureteroscope was used to treat ureteric calculi which did not pass spontaneously after at least 4 weeks of conservative treatment; 181 patients with 183 calculi were treated.

Of 177 ureteric calculi, 29 were in the upper ureter, 44 in the middle and 110 in the lower ureter. The results of treatment showed that there was complete fragmentation in 161 calculi. There was reduction of stone size in 18 but fragmentation was inadequate in 10.

Complications included 3 perforations of the ureter with the endoscope and some minor bleeding for which forced diuresis was sufficient; 15 stones were flushed into the upper urinary tract and then treated by ESWL or PCN.

In ESWL treatment of ureteric calculi *in situ*, approximately 15% of the stones are not suitable for ESWL and ureteroscopic treatment should be the first choice. We consider laser lithotripsy to be an efficient and atraumatic manoeuvre for use with 6 F miniscopes and we prefer this treatment to ultrasound lithotripsy or loop extraction.

## Paediatric Urology

### The Role of DMSA Isotope Studies in Paediatric Urology

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$^{99m}$Tc dimercaptosuccinic acid (DMSA) is a radiopharmaceutical which localises in the proximal tubular cells of the renal cortex, allowing visualisation of functioning renal parenchyma. Intravenous urography (IVU) was the diagnostic tool classically used to evaluate the kidneys. $^{99m}$Tc DMSA studies overcome some of the problems of IVU and have several advantages. They are not affected by overlying bowel gas, no patient preparation is required, no risks due to the contrast medium are encountered and the renal parenchyma is better visualised.

We have applied this diagnostic technique to 3 groups of patients: (1) the detection of acute pyelonephritis; (2) evaluation for the presence of reflux nephropathy; (3) the assessment of renal allograft. We studied 66 previously well children with acute urinary tract infection (UTI) who had DMSA studies performed within 72 h of presentation.

The studies were abnormal in 33 children (50%). The scan appearances improved or became normal in most children re-examined 3–6 months later; 14/47 children who had micturating cystourethrography were found to have significant vesicoureteric reflux (VUR) (grades 2–5); of these 14, 12 had abnormal DMSA scans and the remaining 2 had dilated upper tracts on ultrasound examination.

It was concluded that the incidence of DMSA abnormalities at the time of acute UTI was high (50%); there was a tendency for these abnormalities to resolve with time; an abnormal DMSA scan at the time of UTI identified most children with significant VUR and it would appear that a combination of ultrasound and DMSA scan identified them all.

### Postnatal Outcome of Antenatally Diagnosed Urinary Tract Abnormalities

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Antenatal ultrasound is performed in approximately 80% of pregnancies in South Australia. The incidence of significant congenital abnormalities is 5%, of which 15% are related to the urinary tract. The most common abnormality is dilatation of the renal pelvis—this may represent pelviureteric junction obstruction, multicystic dysplastic kidney, vesicoureteric reflux or an abnormality in a duplex kidney. Frequently on postnatal investigation the dilatation of the renal pelvis is either not significant or resolves spontaneously, suggesting that it is more a physiological phenomenon.

Other abnormalities of the urinary tract such as a dilated ureter, thick walled bladder which fails to empty, or absent bladder may also be identified. Postnatal investigation involves renal and bladder ultrasonography, DTPA diuretic renal scanning, micturating cystourethrography and rarely intravenous urography.

With antenatal ultrasound it is not always possible to predict accurately the anatomical abnormality or functional capacity and one must therefore treat the pregnant mother, father and future child with a realistic, individualised and expectant approach.

### Recent Advances in Management of Wilms' Tumour

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Wilms' tumour was one of the first tumours where chemotherapy had a marked influence on cure. A combination of surgery, chemotherapy and radiotherapy results in about 90% cure, and even with established metastases cure is achieved in about 50% of patients.

Studies have therefore been pursued in 4 directions: indicators for predicting favourable versus unfavourable outcome, genetic factors in predicting the development of Wilms' tumour, the management of bilateral Wilms' tumour, and the reduction of long-term disability by restricting surgery, chemotherapy and radiotherapy to the least necessary. A favourable outcome is closely related to histological factors which make up the group of Wilms' tumours. This seems to be the most important single predictive feature.

A gene locus has been identified associated with Wilms' tumour and a locus nearby is probably involved with some of the associated conditions known to occur with Wilms' tumour. Bilateral Wilms' tumours have been treated successfully with chemotherapy and local surgery, although there may be a place for bilateral nephrectomy and renal transplantation. Minimising therapy has already involved less radiotherapy, less prolonged chemotherapy, or even no chemotherapy at all, and an occasional local excision rather than total nephrectomy.

## Radionuclide Investigation of the Dilated Urinary Tract

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The dilemma of which patient with a dilated or partially obstructed urinary collecting system will benefit from surgical intervention is often difficult. The intravenous urogram, ultrasound and CAT scan provide evidence of dilatation but do not provide objective evidence of obstruction. The diuretic radionuclide renal scan (DRS) and pressure perfusion studies are the best methods available to provide this distinction between obstruction and non-obstructed dilatation.

The DRS measures the resistance to the outflow of urine. During the conventional $^{99m}$Tc DTPA scan for differential renal analysis, frusemide 1 mg/kg is given intravenously and drainage assessed by measuring the rate of clearance and percent decrease of tracer. Our experience in 206 studies correlated with IVU, surgery and long-term follow-up over 8 years and a further 800 diuretic studies has confirmed other reports which favour interpretation of washout curves based on calculated half clearance times and not on the subjective appearance of the curves alone. Our data show a sensitivity of 92%, specificity of 96% and accuracy of 96% for determining significant obstruction.

The literature reports indeterminate or false positive results in up to 15% of patients. This group usually has low grade obstruction, reflux, post-operative dilatation, massively dilated urinary systems or very poor renal function where the kidney does not respond to the diuretic stimulus. To evaluate further this group we have devised the volume expansion diuretic renal scan (VEDRS).

The technique offers the physiological concept of the pressure perfusion study (*i.e.* increased flow through the urinary tract to accentuate obstruction). By infusing 0.9% saline intravenously prior to the renal scan a saline diuresis is stimulated which stresses the urinary tract over a longer period of time and this is accentuated by a bolus injection of intravenous frusemide during the renal scan. The technique has been shown to improve the accuracy of the DRS, particularly in the post-operative dilated group of patients and those patients with markedly dilated systems. The technique is not of value in patients with poorly functioning kidneys.

A decision on whether surgery is warranted can be made in the majority of cases using the DRS and VEDRS to ascertain whether obstruction is present. The radionuclide tests are quantitative and much less invasive than the pressure perfusion studies but require careful interpretation.

## DMSA Scanning in Infants—A Retrospective Study

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DMSA scanning has been shown to be more sensitive than intravenous urography (IVU) or ultrasound in the detection of renal scarring in children with vesicoureteric reflux (VUR). Most reports include children of all ages. In this retrospective analysis, 113 children under the age of 1 year underwent DMSA scanning and the scans were reviewed for areas of decreased uptake consistent with renal damage.

In 86 infants presenting with urinary tract infection (UTI), abnormal scans were present in 34/57 who developed fever and in 12/29 who did not. Of the 67 kidneys with abnormal scans, only 18 had IVU changes of reflux nephropathy. Three kidneys were abnormal on IVU without corresponding scan changes. The remaining 27 infants had undergone investigation for other reasons such as a family history of VUR and none had a history of UTI. Abnormal scans occurred in 15/53 kidneys of which 4 were abnormal on IVU. Amongst the 113 children, 187/224 kidneys had VUR and of these 63 had an abnormal scan in those with higher grades of VUR. Abnormal scans were present in 9 of the 33 kidneys without VUR.

It was concluded that DMSA scanning is more sensitive than IVU in the early detection of renal scarring in infancy.

There is no relationship between the severity of symptoms in infants with UTI and the development of abnormal DMSA scans. There was an increased incidence of abnormal DMSA scan with higher grades of reflux. The presence of abnormal DMSA scans in infants without a history of UTI suggests that renal scarring can occur with sterile reflux.

## Paediatric Uroradiology—The Role of Ultrasound 1990

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With the development of high resolution real time ultrasound, ultrasound has become increasingly important in diagnostic investigations. In our tertiary referral paediatric centre ultrasound is now the baseline investigation for any urinary tract problem in children. Several points of technique need emphasis.

No patient preparation is required apart from ensuring that all children under 2 years are brought along hungry so that they may have a bottle or something to eat during the examination and are more relaxed and easier to examine. Rarely a child may need sedation and an empty stomach is essential for this.

High resolution (5–7 mHz) real time equipment with good near zone resolution is required to examine babies and young infants adequately. Personnel must be experienced in dealing with children. The bladder is examined first, to exclude related lesions and the distal ureters. Whenever possible, the patient is asked to empty the bladder before the kidneys are examined in the coronal sagittal (prone) and transverse planes, with particular emphasis on the parenchyma of the upper and lower poles and on getting a maximum lenght in the sagittal (prone) plane.

We use ultrasound routinely in antenatal diagnosis and in the evaluation and follow-up of vesicoureteric reflux. Children with infections, haematuria, abdominal masses and enuresis are now submitted to ultrasound before other radiological evaluation is contemplated.

### Endoscopic Treatment of Vesicoureteric Reflux with Bovine Collagen

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Austria

Injection with collagen has been performed in 36 girls and 9 women with 70 refluxing ureters. The girls were aged between 1 and 13 years, the adults between 24 and 50 years. All patients had a history of recurrent urinary tract infection and had received chemotherapy on either an intermittent or a long-term basis. Most reflux was grade I–III; only 4 ureters showed reflux grade IV. Three of the children and 4 women had kidneys with pyelonephritic scars.

The follow-up period was 6–24 months. Immediately after intervention, all children were free from reflux. After 3 months, 48 of the 70 ureters showed no reflux, *i.e.* in 22 a recurrence was noted. In 18 ureters the injection was repeated, rendering 12 free of reflux; 4 ureters have not yet been reinjected. The follow-up time of the cured 60 ureters was 6–12 months for 29, and 12–24 months for another 30.

At present, 60 of the 70 ureters are cured by collagen (86%). All ureters with grade IV reflux had a recurrence. One double ureter with reflux had a recurrence.

Thus it is possible to correct most cases of low grade reflux with this method for a considerable time, if not permanently. This may end the discussion on whether operative or conservative treatment should be used in these patients. As long as the orifice is sealed by collagen no long-term chemotherapy is necessary. Collagen does not seem to be a substitute for surgery in high grade reflux.

### Diagnosing PUJ Obstruction—Further Pitfalls

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On a diuretic renal scan, the half-time clearance ($T_{1/2}$) is accepted as showing obstruction if $>1200$ s; $T_{1/2}$ $<900$ is non-obstructed and $T_{1/2}$ between 900 and 1200 s is equivocal. Using perfusion-pressure criteria (Whitaker test), pressure $>20$ cm of water is obstructed, $<15$ cm of water non-obstructed, and between 15 and 20 cm of water equivocal. Combining the tests may not resolve the question in a particular patient. Previous studies by the author have shown 2 basic forms of obstruction: pressure-dependent and volume-dependent.

Fourteen patients (age range 4 days–60 years) with a provisional diagnosis of PUJ obstruction were studied pre-operatively by a diuretic renal scan. At surgery, following rehydration the relative renal pressure (RP) was measured before and after I.V. Lasix (0.5 mg/kg). A pressure greater than 20 cm of water was considered obstructed.

In 8 cases the $T_{1/2}$ was greater than 1100 s and considered obstructed.

In 6 cases the RP was 25 cm of water or greater, and in 1 case was 20 cm of water. Pressure studies could not be performed on 1 patient.

In 6 cases the $T_{1/2}$ was less than 900 s but surgery was performed on clinical grounds.

In 5 of these the RP was greater than 20 cm of water and in the last case a Whitaker test showed a pressure of 28 cm of water. It is suggested that these 6 patients had volume-dependent and therefore intermittent obstruction.

## Bladder Outlet Obstruction and Urodynamics

### Bladder Contractility Assessments: A Brief Review

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Obstruction can be defined as a restriction to flow and/or an impediment to efficient emptying. The bladder responds to the increased outlet resistance by raising its pressure. However, this is not always true. It is likely that around 20% of patients undergoing TURP are not obstructed in the accepted meaning of the term, but have a low flow-low pressure syndrome, which may signify a poorly contracting bladder. The results of TURP in this group are compromised. Attempts to measure contractility both *in vivo* and *in vitro* are being sought.

In clinical voiding studies a method of measuring the power of the bladder (WF) has been developed, based on the Hill equation. Velocity of contraction is calculated on line from the flow rate and instantaneous bladder volume. The curve of WF during voiding is not constant and the maximum (WFmax) can be used for comparisons. Phase plot analysis measuring the rate of change of force against that force enables curve extrapolation to give a theoretical parameter "U" (the maximal dF/dt). While this has no physiological significance, the U parameter normalised to the circumference of the bladder (U/1) correlates well with the WF parameter and is much easier to measure. These parameters seem to be worth further study. Van Mastrigt and Rollema (1988) showed that the U/1 was higher in the obstructed patients than in those not obstructed. There was also a significant reduction in the U/1 after TUR in the obstructed group, but no change in the unobstructed group.

*In vitro* study of contractility of detrusor muscle strips relies upon determining the maximum force the strip can develop under chemical or electrical stimulation.

Velocity is more difficult to measure but is necessary if the contractility of the strip in terms of the Hill equation is to be determined (force alone is inadequate). The quick release method has poor reproducibility.

Combined Force-Velocity Analysis similar to the clinical stop-test can estimate both force and velocity. It has been shown in our laboratory to be accurate and reproducible. The velocity at shortening is preset and normalised and force is determined. Repeated at different velocities a force velocity curve is constructed. The intercepts Fmax and Vmax are contractility parameters which can be compared between different strips in different patient groups.

Studies of this kind indicate the need to be more critical in the evaluation of the apparently obstructed patient.

## Reference

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## Bladder Neck Obstruction

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The evaluation of urodynamic function by symptoms, clinical examination and endoscopy is notoriously unreliable. For more than 20 years we have been evaluating problems of voiding by means of synchronous video pressure flow cystourethrography.

A finding of high pressure—low flow voiding in the younger male patient is frequently associated with observed failure of the bladder neck to relax during bladder contraction—bladder neck dyssynergia. In-depth questioning of the patient frequently reveals that this is a lifelong problem and there is some evidence that it is related to increased sympathetic activity, and may on occasion be associated with prostate hypersensitivity or "chronic prostatitis".

It is important to appreciate that a dyssynergic bladder neck cannot be diagnosed endoscopically. Generalised hypertrophy of a bladder secondary to any form of distal obstruction, such as a urethral stricture, will result in a hypertrophied prominent bladder neck together with a typical appearance of bladder trabeculation; however, if studied urodynamically it will be found that this bladder neck opens normally during bladder contraction.

Iatrogenic failure of bladder neck opening may occur as a result of the addition of an enterocystoplasty to a previously normal detrusor/bladder neck opening mechanism

Similar problems with failure of bladder neck opening may also occasionally be seen in patients with low detrusor activity for other reasons. In this group may be included the rare cases of female bladder neck obstruction.

Objective urodynamic pressure flow measurements are essential to diagnose this difficult group of younger "non-prostate" patients with persistent lower urinary tract symptoms.

## Sphincter Dyssynergia

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The distal urethral sphincter mechanism (DSM) is made up of adrenergically innervated smooth muscle and somatically innervated striated muscle. During normal micturition the DSM relaxes just prior to the onset of a co-ordinated and sustained detrusor contraction which expels urine from the bladder through the relaxed outlet. After emptying, the detrusor relaxes and the urethral pressure is restored by resumption of tonus in the rhabdosphincter. This normal sphincteric synergic activity during the micturition reflex is co-ordinated from the mesencephalic pontine centre for micturition.

### *Neuropathic dyssynergia*

Neurological lesions which disrupt the integrity of the long tracts from the pons to the detrusor and pudendal nuclei in the S2/3 segments of the spinal cord result in inco-ordination of the normal vesicourethral reflexes. In such cases, although the detrusor still develops co-ordinated (and hyper-reflexic) contractions, synchronous urethral relaxation is missing and micturition occurs through an obstructive urethra. This is the classic detrusor-sphincter dyssynergia which causes devastating consequences on the remainder of the urinary tract if not managed properly.

Inco-ordinated micturition also occurs when a conus, cauda equina or pelvic nerve lesion decentralises the bladder and urethra. The bladder may become areflexic and acontractile but residual activity in the smooth muscle of the DSM may still result in the urethra being obstructive relative to the inability of the detrusor to generate a co-ordinated and expulsive contraction. This is isolated sphincter obstruction rather than true dyssynergia but may still have important urological consequences.

*Sphincter active voiding dysfunction*

Failure of the DSM to relax synchronously with a voiding detrusor contraction may occur in the absence of neuropathy. Painful urination in children is commonly associated with staccato micturition, or sometimes results in retention. This type of voiding dysfunction may occur as part of a learned behavioural problem in children with detrusor instability. Often it is associated with urinary tract infections due to incomplete bladder emptying. The common habit in women of "hovering" over the toilet may result in such a voiding dysfunction and may be a factor in the increased tendency of women to develop urinary tract infection.

## Endoscopic Bladder Neck Incision

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The only indication for bladder neck incision must be the need to relieve a urodynamically proven bladder neck obstruction. The bladder neck, in both male and female, is one of the vital continence mechanisms and good evidence of obstruction must be obtained before it is attacked surgically.

A unilateral endoscopic bladder neck incision using a Collins electrode is a simple, safe and rapid method of treating a dyssynergic bladder neck. We carry out the incision at 4 or 5 o'clock. In order to decrease the incidence of retrograde ejaculation it is important not to incise too far proximally into the bladder or distally into the prostatic urethra. All that is necessary is to incise through the thickened ring of dyssynergic bladder neck muscle which tends to spring apart as it is cut through into the extravesical fat.

Results of this simple procedure are excellent; relief of obstruction can be assured, although there is a 10 to 20% incidence of reflux ejaculation. We have rarely seen a late recurrence of obstruction following this procedure, although of course prostate obstruction may occur in later years. For this reason in the older patient it is reasonable to extend the incision distally into the prostate.

It is of interest that when these patients are reviewed urodynamically after a bladder neck incision, although the bladder neck opens widely on voiding it is usually occlusive at rest.

## Prospective Urodynamic Review of Prostatectomy for BPH

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Prostatectomy, the most common urological operation, is generally regarded as a safe procedure with little morbidity and excellent results, but in recent years the accuracy of this view has been challenged. To assess in detail the outcome of the operation and to evaluate the role of urodynamic tests in selecting patients for prostatectomy, a prospective study has been conducted in 217 men undergoing elective surgery for bladder outflow obstruction; 189 underwent endoscopic prostatectomy, 9 retropubic prostatectomy and 19 bladder neck incision. The mean age of the patients was 69 years. The average duration of symptoms was 2.3 years, the mean weight of resected tissue 23 g and 24 patients were found to have incidental prostate cancer.

All patients were selected for prostatectomy on clinical grounds and had a peak flow <15 ml/s. In addition, all patients had full video-urodynamic assessment prior to surgery but the results of this were not divulged to the surgeon. Post-operatively all patients completed a symptom questionnaire, 182 had full urodynamic evaluation, 26 agreed to measurement of flow and residual urine only and 164 were reviewed jointly by a general practitioner and an independent urologist.

At follow-up 54% were symptom-free and 25% had minor symptoms that did not interfere with lifestyle. However, 16% had significant residual symptoms, 4.6% reported no improvement and 0.4% were worse. Considering all forms of post-operative assessment, 71% were judged to have a satisfactory outcome but 29% were unsatisfactory: 15% with persistent urgency or incontinence, 12% with persistent poor flow and 2% with stricture or bladder neck stenosis. The effect of prostatectomy on sexual activity was not examined.

Pre-operative predictors of a poor outcome were urge incontinence, low voiding pressure, low urethral resistance, detrusor instability and small prostate size. Multivariate analysis of pre-operative urodynamic parameters was disappointing as the best "discriminant function" was 48% sensitive and it was concluded that urodynamic measurement did not predict outcome accurately for individual patients.

For detailed discussion of this study see Neal, D. E., Ramsden, P. D., Sharples, L. *et al.* (1989). Outcome of elective prostatectomy. *Br. Med. J*, **299**, 762–767.

## Pilot Study into Microwave Hyperthermia of the Prostate

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The "Prostathermer" (Biodan Corporation) uses a transrectal microwave applicator to heat the prostate to the range 42–44.5°C. The device was used to treat the prostate of patients with outflow obstruction, abacterial prostatitis and carcinoma of the prostate. The treatments were performed entirely as out-patient procedures without anaesthesia other than intraurethral lignocaine gel. Each treatment consisted of 6 sessions of 1 hour's duration.

*Outflow obstruction.* Three patients had an indwelling catheter, having failed to void after attempted removal. All 3 managed to void after hyperthermia. Twenty patients had outflow obstruction proven urodynamically. The pre-treatment mean flow rate of 7.3 ml/s was increased immediately after treatment to 12.3 ml/s. The post-micturition residual urine was reduced from a mean of 166 to 62.5 ml.

*Abacterial prostatitis.* Ten patients were selected because of severe and continuous discomfort present for 6 months without interruption. All felt some improvement from the therapy; 7 of these patients had a dysfunctional voiding pattern which returned to normal during treatment. One patient has relapsed after 3 months with a return of dysfunctional voiding.

*Carcinoma of prostate.* Four patients had extensive carcinoma of the prostate without bone metastases.

Only 1 had a significant response with a fall in PSA and ultrasonic evidence of shrinkage. This patient had previously had radioactive seeds. The 3 patients who failed to respond had had no other treatment.

## A New Treatment for Prostatic Obstruction: the Permanently Implanted Urethral "Wallstent$^R$"

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Despite recent developments in endoscopic and reconstructive urology the treatment of urethral strictures is still far from ideal. We have been using a new urethral stent for implantation into strictured urethras. The stent was originally developed for endovascular use and is woven in the form of a tubular mesh of fine stainless steel wire. The elastic properties of the mesh hold it against the wall of the urethra, allowing urothelium to grow over the implanted material which becomes incorporated within the wall of the urethra while holding open the strictured area.

We have successfully treated 32 patients with recurrent strictures of the bulb and proximal penile urethra. The only failure has been in a patient with a complete rupture of the bulbar urethra. In all cases the stent was covered completely with urothelium between 4 and 6 months after insertion. We have also used the stent successfully in sphincter strictures and dyssynergic strictures in conjunction with the artificial urinary sphincter. The stent has also been particularly useful in spinal injury patients as an effective alternative to sphincterotomy.

Following recent anxiety about the risks associated with prostate surgery in the elderly patient we have used the Wallstent for the treatment of 40 patients with prostate obstruction. Most of these patients presented with acute urinary retention and were unfit for other surgical procedures. The stents were inserted endoscopically under local anaesthesia; 38 patients were very satisfied with the procedure and are passing urine satisfactorily; 1 continued to have severe symptoms from detrusor instability and 1 failed to pass urine because of prostate tumour obstructing the membranous urethra.

Although follow-up is limited to 3 years it does seem that this new urethral stent offers a simple, safe and effective treatment for many patients with bladder outlet obstruction.

## Flow Rates Following TUR: A Multicentre Trial to Demonstrate Electronic Communication Techniques

S. P. Gowland
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A multicentre international trial was undertaken to determine effective maximal flow rates before TURP, immediately after operation and at follow-up approximately 6 weeks after discharge from hospital. The plan was to document the often heard statement by patients that the flow rate appeared better immediately after operation than at the time of the first post-operative visit.

A new technique using modern computer communications was used to link multiple centres around the world. We believe the technique we have refined will not only enable non-technical people with computers to participate but will vastly improve the management of the multicentre trial, the concept of which has tended to fall into disrepute for logistical reasons. Isolated practitioners will no longer be disadvantaged if they wish to join such trials with our system.

During the trial the participants can easily communicate with the trial centre in Christchurch and with each other by electronic messaging.

Trial result data are returned monthly electronically and the accumulated results are available in an analysed form a day or two later. Raw accumulated trial data are also available for participants who wish to run their own analysis programes.

## Out-Patient Transurethral Balloon Urethroplasty

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Transurethral balloon dilatation has been performed on 6 patients in an out-patient setting. All were suffering from obstructive symptoms but none was in retention. They were assessed before and after the procedure on symptomatic and urodynamic criteria. The dilatation was performed with a 30-mm diameter balloon inflated for 15 min. No major complications resulted from the procedure and no patient required admission to hospital.

Follow-up has been on average 11.7 months. No patient had a successful result at 6 weeks, despite early initial improvement in 5 patients. Four patients have subsequently required transurethral resection of the prostate; the other 2 were no better than prior to treatment but declined further treatment.

In view of our results and reports from other centres we cannot recommend transurethral balloon dilatation of the prostate in patients with bladder outlet obstruction due to benign prostatic hypertrophy.

## Stone Disease

### New Trends in Medical Evaluation and Treatment of Patients with Urolithiasis

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Urolithiasis is a significant problem with a recognised incidence of 12–15% in various series. Men form stones twice as often as women and racial differences exist in that urolithiasis is 3–4 times more common in whites than blacks. Stone formers are divided between those forming a stone for the first time and those with active recurrent disease, *i.e.* evidence of stone formation and growth within the past year. A more thorough evaluation is generally carried out in the latter group to define various metabolic problems.

Causes of calcium-containing stones and their relative frequency include hypercalciuria 30–60%, hyperuricosuria 15–20%, hyperoxaluria 10–15% and hypocituria 10–20%. Other causes include hypomagnesuria and heterozygous cystinuria. Many patients have more than 1 definable metabolic abnormality. Struvite stones comprise 5–10% of all calculi and are associated with infections with urease-producing bacteria. It is important to remember that 50% of these patients have a definable metabolic problem.

Uric acid stones comprise 5–10% of all stones and the primary metabolic problem relates to the presence of a persistently acid urine, usually in the range of pH 5.0. Other predisposing causes result from hyperuricosuria and the presence of a highly concentrated urine. Cystine stones are responsible for approximately 1% of stones. Cystinuria is inherited as an autosomal recessive trait.

Treatment involves increasing urinary volume and decreasing the solute load by both dietary and medical therapy.

### Low Molecular Weight Inhibitors and Calcium Oxalate Stone Formation

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The potential role of inhibitors in calcium stone formation is not trivial: it may account for the fact that stones do not occur in the presence of significant urinary supersaturation. Although macromolecules have been shown to contribute to the inhibitory effect of urine on calcium oxalate (CaOx) crystallisation, low molecular weight inhibitors are, for the time being, of greater potential value because this concentration in the urine can be raised relatively easily. The aim of this study was to test the effects of therapeutic urinary concentrations of pyrophosphate, citrate and magnesium on CaOx crystallisation in undiluted human urine from which the macromolecules had been removed.

Urine samples were collected from normal men and pooled. The pooled collections were then divided into 3 parts. One of these was spun (10000 × g) and filtered (0.22 μm), a second was ultrafiltered (10000 Da) and the third was similarly ultrafiltered, but in addition was supplemented with amounts of pyrophosphate, citrate or magnesium which could be realistically achieved during treatment.

Thus the pyrophosphate concentration was increased by 75 μmol/L, the citrate concentration by 4 mmol/L and the magnesium concentration by 4 mmol/L.

Crystallisation was induced in the samples by the addition of a defined oxalate load above the metastable limit determined by titration with oxalate, and crystal size and volume were determined by Coulter Counter analysis. Crystalline material deposited was examined using scanning electron microscopy (SEM).

Ultrafiltration had no effect on the metastable limits of the urines, but in all cases crystals precipitated from the ultrafiltered urines were significantly more highly aggregated than those from the spun and filtered urines, which still contained a high concentration of macromolecules.

The addition of pyrophosphate and citrate did not alter the urinary metastable limits or reduce the degree of aggregation of the precipitated crystals. However, in both cases the amount of crystalline material deposited was markedly reduced. Magnesium, though showing the same effect on the amount of CaOx deposited and the degree of aggregation, also significantly raised the urinary metastable limit, thereby indicating that it strongly inhibited crystal nucleation.

It was concluded that low molecular weight inhibitors fulfil a role complementary to that of urinary macromolecules. The latter strongly inhibit crystal aggregation but have little effect on the amount of crystalline material deposited. Pyrophosphate, citrate and magnesium, on the other hand, while having no effect on crystal aggregation, significantly reduce the amount of crystalline CaOx deposited.

They may therefore be instrumental in reducing stone formation *in vivo* and may be of potential benefit in the treatment of CaOx stone recurrences.

## Crystal Matrix Protein—An Inhibitor of Calcium Oxalate Stone Formation?

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It is well recognised that approximately 2–6% of the dry weight of stones that have calcium oxalate as their principal component is organic material referred to as the matrix. The abundance of protein in the matrix has fuelled speculation and controversy regarding the possible role of protein in urolithiasis. The most important events in stone formation may be those that lead to the formation and lodging of a nidus in a kidney tubule. Thus the aim of this study was to characterise the composition and the role of the proteins associated with the early stages of calcium oxalate crystallisation in urine.

Calcium oxalate crystallisation was induced in normal urine by the addition of an oxalate load. The crystals were harvested, demineralised with EDTA, and the proteins associated with the crystals separated and characterised using sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) and Western Blotting.

The majority of urinary proteins exhibited little or no affinity for calcium oxalate crystals.

The predominant protein associated with the crystals had a molecular weight of 30,000 daltons and was designated "crystal matrix protein" (CMP).

This protein could not be visualised in the whole urine electrophoretic patterns and appears to be a minor urinary constituent with an avid affinity for calcium oxalate. Western blotting suggested that CMP is a previously unknown urinary constituent.

The effect of CMP (10 mg/l) on calcium oxalate crystallisation was tested *in vitro* in ultrafiltered urine using a Coulter Counter to record the particle size distribution of the crystals. Results were substantiated by scanning electron microscopy.

Crystal aggregation was completely abolished in the presence of CMP, causing a marked reduction in the mean size of the crystalline particles from 13 μm in the control to 6 μm.

It was calculated that the majority of urinary proteins play no role in calcium oxalate crystal formation. One protein, CMP, exhibits a remarkable affinity for calcium oxalate crystals. *In vitro*, this protein is a potent inhibitor of crystal aggregation and may therefore be important in preventing stone formation *in vivo*.

## Shockwave Lithotripsy of Ureteric Calculi—How Efficient is Localisation with Ultrasound?

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The Dornier MPL 9000 has been used at our interdisciplinary shockwave centre for both urinary and biliary lithotripsy since January 1989. ESWL of renal calculi under ultrasound guidance quickly became a routine procedure, whereas *in situ* treatment of ureteric calculi was found to be difficult. Patients with ureteric calculi represent about 40% of our stone patients. In order to evaluate the usefulness of ultrasound localisation for *in situ* ESWL of ureteric calculi, we set up a clinical trial to determine whether visualisation of ureteric stones was possible by ultrasound and, if so, whether localisation and focusing of the stone were feasible on the lithotriptor.

Thirty consecutive patients have been evaluated; 12 had proximal and 18 had distal ureteric calculi. Overall, only 30% of all stones (upper 16%, lower 39%) could be clearly identified by ultrasound. All investigations were carried out by the same physician, who had considerable experience with diagnostic ultrasound.

All patients with ultrasonically detectable stones were treated with the MPL 9000, the stone being both localised and focused.

However, ultrasound detection of ureteric calculi is the exception rather than the rule. Consequently, a fluoroscopic C-arm has been added to the localisation facility of the MPL 9000. A study is under way to evaluate the treatment and localisation capabilities of this combination.

## ESWL Management of Distal Ureteric Calculi

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The management of distal ureteric calculi can be difficult. The results of 67 patients referred with distal ureteric calculi were evaluated after treatment on the Dornier HM3 lithotriptor. Distal ureteric calculi were classified as those at or distal to the proximal margin of the sacro-iliac joint. In 11 patients the calculi overlay the sacro-iliac joint while in the remaining 56 patients the stones were distal to the distal margin of the sacro-iliac joint.

Patients with stones overlying the sacro-iliac joint were treated prone and those with stones distal to the sacro-iliac joint were treated in the saddle (astride) position. After 1 session of lithotripsy, 41 patients were completely stone-free at 3 months. A further 5 patients had a second session of lithotripsy and this was successful in 3. Of the 64 patients in whom follow-up was available, 44 (69%) were therefore rendered stone-free by ESWL.

Eight patients had manipulations for residual fragments 3 months after lithotripsy and 12 patients with residual fragments are currently under surveillance by their urologists. Three patients were lost to follow-up.

Lithotripsy has proved an effective treatment for distal ureteric calculi and has rendered 69% of patients stone-free with minimal morbidity.

## Is Retrograde Ureteric Manipulation Still Needed in the Primary Treatment of Ureteric Calculi?

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Experience with the management of ureteric calculi in 1240 reno-ureteric units during a 28-month period revealed that 81% can be treated by ESWL *in situ* with second-generation lithotriptors. Success rates of 90, 69 and 82% were achieved for stones in the proximal, mid and distal third of the ureter, with auxiliary measures needed in 10% of patients and 86% stone-free after 3 months. In contrast, attempts to manipulate stones in the proximal or mid-ureter back into the kidney and to treat them by ESWL were successful in only 86 and 76% respectively of the reno-ureteric units, with auxiliary measures required post-operatively in 22% and 83% of the kidneys stone-free after 3 months. In spite of the availability of ultra-thin ureteroscopes and ultrasonic, electrohydraulic and laser lithotripsy, ureteroscopy was ultimately used in only 9% of all patients, mainly for removing impacted stones in the segment of ureter overlying the bony pelvis, where they cannot be treated *in situ* or dislodged. The procedure was immediately successful in 86% of the patients, and in another 8% after a second attempt, complications of a moderate degree occurred in 11% and failure in 1%.

Since ESWL *in situ* does not require anaesthesia, is minimally invasive and only marginally less effective than the more aggressive approaches, it should be the first choice of treatment. Retrograde ureteric manipulation should be limited to situations where ESWL *in situ* fails.

## Results of Treatment of the First 250 Patients Receiving ESWL on a Technomed Sonolith 3000 Lithotriptor

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A regionally based lithotriptor service was introduced into the West Midlands region in April 1989 with the installation of a Technomed SONOLITH 3000 lithotriptor.

The results of treatment of the first 250 patients receiving lithotripsy on this machine have been analysed.

Virtually every treatment was performed without general anaesthesia and on an out-patient basis. An effective sedo-analgesic regime permitted comfortable treatment for all patients. There has been a high single treatment rate and a corresponding low re-treatment rate. Serious complications were very few. The surgical intervention rate following treatment was low and very few stones failed to fragment. Lithotripsy performed on the SONOLITH 3000 has proved to be a safe and effective treatment. The machine is simple to use and has been very reliable.

# Keith Kirkland Prize

## Contractility of Detrusor Muscle from Patients Undergoing Elective Transurethral Resection of the Prostate

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The assessment of contractility of the bladder using the urodynamic stop-test in patients with prostatic obstruction has yielded conflicting results which have been attributed to the unphysiological nature of this test. An *in vitro* study is presented which compares the contractility of these muscle strips from clinically obstructed patients with similar muscle samples from unobstructed patients. The contractility of these muscle strips is defined in terms of the force-velocity relation and yields both static (force) and dynamic (velocity) parameters. This is derived by the method of van Mastrigt using an *in vitro* analogue of the stop-test.

The study involved 50 male patients; 25 were clinically obstructed and undergoing elective TURP. The remaining 25 were unobstructed (PFR >15 ml) and age-matched. Small muscle strips (1 × 3 mm) were obtained from cup biopsies of the bladder from each patient. These were placed in an organ bath continuously perfused with oxygenated Krebs solution. Electrical stimulation and simultaneous muscle shortening via a voltage ramp generator yielded a normalised force for each preset velocity.

Seven different points on the force-velocity curve were then measured and a hyperbolic curve was fitted to the data for each muscle strip. The intercepts of this curve represent the contractility parameters derived for each strip of muscle, *i.e.* Fmax (isometric force) and Vmax (maximum velocity at zero force). The cross-sectional area of each strip was estimated by a computer-assisted morphometric technique and the collagen content of detrusor muscle from each patient was assessed by biochemical hydroxyproline analysis.

There was no significant difference in the isometric force (F Max) corrected for cross-sectional area between either the obstructed (mean 2.57 ± 0.39) or unobstructed groups (mean 2.98 ± 0.43). The length-corrected maximum theoretical velocity (Vmax in mm/s) was significantly slower ($P<0.01$) in the obstructed (mean 0.19 ± 0.01) compared to the unobstructed group (mean 0.29 ± 0.02). This difference could not be explained by collagen deposition, as has been suggested by others, since this was similar in both groups (4.1 vs 3.5%).

This study demonstrates that there is already an intrinsic abnormality in the contractile function of detrusor muscle of patients by the time they present for TURP.

### Expression of the $T_n$ Antigen in Transitional Cell Carcinomas

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Expression of the $T_n$ antigen (N-acetyl galactosamine O-glycosidically linked to serine or threonine) is common in a wide variety of cancers. Using immunohistochemistry and FBT3, a monoclonal anti-$T_n$ antibody, fixed material from bladder tissue was studied to detect the expression of the $T_n$ antigen. Expression was found in 37 of 75 different histological grades of transitional cell carcinomas studied (2/12 T1, 2/5 T1/2, 15/26 T2, 6/9 T2/3 12/14 T3) but not in 9 cases of *in situ* carcinoma or 16 normal specimens examined. $T_n$ antigen may assist in detecting the invasive potential of transitional cell carcinomas.

### Androgen and Epidermal Growth Factor Receptor Status in Benign and Malignant Prostatic Disease

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Androgens are essential for the development and maintenance of the prostate. However, there is also evidence to suggest that prostatic growth may be partially mediated by Epidermal Growth Factor (EGF) and that EGF receptor content is under androgenic control. Androgen ablative therapy is the treatment of choice for Stage D prostatic carcinoma but despite its effectiveness the degree and duration of response are unpredictable and highly variable.

In an ongoing trial, we have characterised the expression of cytoplasmic androgen receptors (ARc), nuclear androgen receptors (ARn) and EGF receptors (EGFR) in 50 consecutive cases of benign prostatic hyperplasia (BPH) or prostatic carcinoma, following transurethral prostatic resection. In both disorders marked heterogeneity of expression was found.

In BPH, expression of ARc ranged from 0–1132 fmol/g tissue (median 316), ARn ranged from 0–330 fmol/g tissue (median 135) and EGFR ranged from 0–213 fmol/g tissue (median 114).

In prostatic carcinoma, expression of ARc ranged from 0–1158 fmol/g tissue (median 212), ARn ranged from 34–316 fmol/g tissue (median 84) and EGFR ranged from 0–712 fmol/g tissue (median 147). These data further illustrate the functional heterogeneity of prostatic disease and yield possible insights into mechanisms of histogenesis.

### Flexible Cystoscopy: An Adjunct to ESWL

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Flexible cystoscopy has been shown to be time-saving and cost-effective in comparison to rigid cystoscopy. Insertion of double pigtail stents using the flexible cystoscope has not previously been reported. Since ESWL has been available, the trend has been toward local anaesthetic out-patient treatment. A new technique for double pigtail stent insertion using the flexible cystoscopy under local anaesthesia as an out-patient has been established. An analysis of its cost effectiveness plus a time comparison was performed.

Forty of 44 patients had successful stent insertions comparable to that by the traditional method. The time comparison showed significant time savings both in theatre and hospital stay. Cost effectiveness analysis was performed by a scenario comparison showing a significant patient saving.

This technique is reliable, quick and cost-effective; it increases the therapeutic role of the flexible cystoscope and compliments out-patients ESWL treatment.

### The Changing Presentation of Renal Carcinoma

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A retrospective chart review was made of the mode of presentation of renal carcinoma in 40 consecutive patients managed from 1977 to 1982, and compared to that of a recent group of 40 consecutive patients presenting between 1987 and 1989. Eleven patients (28%) in the recent group had an asymptomatic tumour diagnosed as an incidental finding on intravenous urography, ultrasound or computed tomography, significantly more than the 2 patients (5%) so found in the earlier group.

In the recent group, 10 of the 11 incidental tumours were confined to the kidney (Stage A) and the other invaded perinephric fat (Stage B), and were of significantly earlier state than symptomatic tumours. The incidental tumours were of significantly smaller diameter than symptomatic tumours of the same stage.

With the increased use of various radiological procedures, over one-quarter of patients with renal carcinoma in our practice presented with an asymptomatic, early stage, small tumour.

## Prostatic Cancer

### Prostatic Cancer: An Overview

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The confusion that undermines the treatment of prostate cancer has been compounded in recent years by the resurgence of radical prostatectomy, ill-founded claims for the superiority of total hormone ablation and the publication of non-randomised data concerning the "natural history" of this disease. The reason for the confusion is the absence of any prospective trials conducted long enough ago with sufficient numbers of patients to allow unequivocal conclusions to be drawn.

It is generally accepted that impalpable, incidental focal prostate cancer does not need immediate treatment, especially if it is well differentiated. Contrary to this practice is the growing interest in screening programmes for prostate cancer which are based upon the philosophy that early treatment for unsuspected cancer would be beneficial. This illogicality begs careful thought.

For disease believed to be confined to the prostate, radical prostatectomy appeals to many urologists and patients. Long-term data from the Mayo Clinic suggest a risk of local or distant progression for 14% and death from prostate cancer of 7% at 15 years. British reviews of untreated patients imply that 36% of patients need no treatment in 5 years and only 4% die from cancer compared with 40% from other causes.

Johansson's prospective review of the natural history of similar prostate cancer in Swedish men reported that 23% needed treatment for progression and 7% died of prostate cancer with a median follow-up of 6.5 years. These "data" suggest that probably 10% of men with confined prostate cancer may live longer if subjected to radical prostatectomy at a time when life expectancy is 15 years, but the true benefit of this operation remains in doubt and the controversy will only be resolved by a large trial which will be difficult to recruit.

It is 17 years since the VACURG studies suggested that treatment for asymptomatic, locally advanced or metastatic prostate cancer could be delayed until disease progression became apparent. Opinions concerning the optimum timing of hormone treatment remain divided. The MRC is conducting a study that compares immediate with deferred hormone treatment in this situation. More than 650 patients have been randomised but many more will be required with longer follow-up before the result is known. The EORTC has commenced a similar study.

Advertisements for antiandrogens claim that patients survive longer with their use. The facts to date are that 3 of 6 multicentre trials report that the addition of Flutamide or Anandron to bilateral orchiectomy or LHRH analogues delays progression by a few months and increases median survival by 7 months. The other studies show no significant advantage so far but further follow-up is awaited. Clearly, total hormone ablation is not the answer for prostate cancer.

A review of deferred treatment in Newcastle showed that 30% of patients did not need treatment during their lifetime or within 5 years. Conversely, 70% needed treatment. The problem is predicting this need. Advanced local stage, the presence of metastases, poor tumour grade, anaemia, poor performance status, pain, elevated prostatic acid phosphatase and prostate specific antigen are all associated with poor prognosis. Instead of recommending the same treatment for all patients it seems logical to tailor different treatments to specific prognostic groups based upon multivariate analyses of these factors. The EORTC is introducing new trials on this basis.

## Significant Prognostic Importance of Nuclear DNA Content Measured by Static Cytometry for Patients with Apparently Localised Prostate Carcinoma Treated by External Beam Radiotherapy

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Nuclear DNA ploidy measured by flow cytometry has demonstrated prognostic value for patients with localised prostate cancer managed by radical prostatectomy. To determine if tumour nuclear DNA content might be of prognostic importance for patients treated by external beam radiotherapy, we used static DNA cytometry performed on small needle biopsy specimens obtained prior to treatment. Tissue specimens were cut to 6 μm thickness and stained by the Feulgen method. DNA measurements were carried out with the Zeiss IBAS 2000 image analysis system. Mean DNA content of normal lymph node cells was used to set a DNA content of 1.0. At least 100 tumour nuclei were measured per specimen.

Thirty-nine patients treated with 60 Gy to the prostate from 1974 to 1978 were studied. All patients had had at least 10 years' follow-up. Group I (17 patients) had a tumour cell relative DNA content of $<1.5$. Group II (22 patients) had a tumour cell relative DNA content of $\geq 1.5$. There were no significant differences in histological grade, Gleason score or adjuvant treatment between the 2 groups.

Thirty-five percent of Group I patients showed clinical evidence of extracapsular tumour extension; 54% of Group II were clinical stage C. None of the patients in Group I (low DNA content) demonstrated evidence of tumour progression. By contrast, 87% of patients in Group II progressed within 10 years ($P<0.00001$). These preliminary data indicate that nuclear DNA content measured by static cytometry may be particularly useful in identifying patients who may benefit from external beam radiotherapy. Confirmation of these data with a larger group of patients is mandatory.

## An American Approach to the Treatment of Localised Prostatic Cancer

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Treatment of stages A and B carcinoma of the prostate is either surgical extirpation or radiation therapy. Surgical removal of the prostate can be accomplished with either a radical retropubic prostatectomy or perineal prostatectomy. For precise staging of the patient either radiotherapy or surgery should be preceded by staging pelvic lymphadenectomy.

A modification of the radical prostatectomy spares the parasympathetic nerves that innervate the corpora cavernosa. Approximately 80% of patients with an intact post-operative prostate capsule determined pathologically will be potent at follow-up 1 year later compared to approximately 40% of patients who had pathologically determined extensive involvement of periprostatic tissue and only 30% of men who had involvement of the seminal vesicles and pelvic lymph nodes. The neurovascular bundle can be sacrificed on one side if tumour is extensive in that region and potency still maintained. It is possible to preserve sexual function in the majority of patients undergoing radical prostatectomy without compromising the adequacy of the cancer operation.

Radiation therapy is a reasonable option for patients with stages A and B disease as well. It includes external beam radiation either to the pelvic area and prostate or solely to the prostate preceded by staging pelvic lymphadenectomy. Generally 50–70 Gy are delivered over several weeks. The advocates of this treatment feel that survival rates compare favourably with those achieved by surgical intervention, although some data seem to support the superiority of the surgical approach. The role of interstitial radiotherapy continues to be investigated.

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## Video Image Analysis of Prostate Specific Antigen and Prostatic Acid Phosphatase Cellular Expression as Predictors of Outcome in Metastatic Prostate Cancer

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The search for a single useful indicator of prognosis in men with metastatic prostate cancer has so far proven fruitless. Prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) are 2 markers commonly perceived to fulfil this role. It is thought that well differentiated tumours produce more of these constituents on a cellular basis than poorly differentiated tumours. High serum levels in stage D2 disease are interpreted as being due to the great bulk of cells present rather than to a good histological grade in the majority of cases. We have retrospectively identified 48 patients with stage D2 disease who underwent orchiectomy and transurethral prostatic resection and who were selected into 1 of 2 treatment outcome groups; 32 patients died within 12 months of surgery and 16 survived over 5 years after orchiectomy; these were designated poor and good outcome groups respectively.

Using a histological grading based on 3 grades (poor, moderate and well differentiated), 256 tumours were poorly, 10 moderately and 12 well differentiated. Using commercially available antisera and standard immunoperoxidase techniques, 5 μm sections of each tissue were stained for PSA and PAP (1:1000 PSA, 1:400 PAP).

Relative quantification of PSA and PAP per tumour was performed using image analysis techniques on random microscopic fields using a ×40 objective and ×0.5 camera eye piece to assess a minimum of 250 cells from both the primary monoclonal antibody-stained and control antibody-stained sections.

Each slide was examined using the Flinders Imaging MD-20 image analysis system comprising microscope, video camera, monitor and digitiser pad linked to a personal computer for data storage and analysis. By employing a combination of threshold setting and manual editing to exclude non-specific background and nuclear staining, objective measurements of cytoplasmic stain density were obtained.

Cellular PAP expression was significantly different between the 2 outcome groups ($P < 0.001$), but considerable overlap of values renders this assessment of little clinical usefulness. PSA expression was not significantly different between outcome groups and was therefore unable to delineate a given patient's prognosis. Although a trend existed with both antigens towards lower expression in the poorly differentiated tumours, no statistically significant association existed between tumour grade and stain intensity.

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## Flow Cytometry in Stage D2 Prostate Carcinoma: A Worthwhile Predictor of Outcome Following Endocrine Manipulation

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The use of flow cytometry has demonstrated that aneuploid prostate cancers are likely to metastasise. More recently, flow cytometric analysis on paraffin-embedded tissues has indicated that DNA ploidy provides highly significant prognostic data in metastatic prostate cancer. In an effort to evaluate this further we have examined 103 patients with prostate cancer using techniques which digest nuclei from paraffin-embedded tissues. All patients had stage D2 metastatic disease and had undergone prostatic resection and orchiectomy. Patients were selected on the basis of survival into 2 groups. Poor survival was indicated by death within 12 months of orchiectomy and good survival as living beyond 5 years after orchiectomy. This represents approximately 30% of stage D2 prostate cancers.

Of 103 tissues examined, 6 proved unsuitable for analysis due to hypo-cellularity of available blocks. Of the remaining tissues, 35 were in the good outcome and 62 the poor outcome group. Ploidy status was a highly significant independent prognostic indicator ($P < 0.001$); 95% of tetraploid and 83% of aneuploid tumours, representing 91% of the non-diploid tumours, were found in the poor outcome group. A corresponding 64% of diploid tumours were found within the good outcome group. Using a tumour grading based on 3 categories (well, moderate and poorly differentiated), significant prognostic information independent of ploidy status could be gained ($P<0.005$), with 65% of well differentiated tumours in the good outcome group and 78% of poorly differentiated tumours in the poor outcome group. Moderately differentiated tumours were evenly distributed between the 2 outcome groups.

When ploidy status was combined with histological grading, additional prognostic groups were defined, varying from a 95% chance of good outcome for the well differentiated diploid tumour to 5% chance of a good outcome for the poorly differentiated non-diploid tumour patient.

Overall, our study has demonstrated that DNA ploidy status determination and tumour grade are significant independent predictors of outcome following orchiectomy which on combination give additional prognostic information.

### 5-Fluorouracil Versus 5-Fluorouracil Plus Folinic Acid in Advanced Hormone-Escaped Prostatic Cancer

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Results of cytotoxic chemotherapy of advanced, hormone-escaped prostatic cancer are disappointing. Some protocols show a good palliative, analgesic effect. One of the best substances used in such protocols is the antimetabolite 5-fluorouracil, with remission rates ranging from 10 to 20%. 5-FU acts via inhibition of the enzyme thymidinesynthetase which catalyses an essential step in DNA synthesis. Co-enzyme of this reaction is tetrahydrofolate (THF). There is a little evidence that exogenous application of THF will result in increased cytotoxic effects of 5-FU.

Three different cell lines of prostatic cancer were incubated with increasing concentrations of 5-FU alone or in combination with THF. Depending on the concentration added, 5-FU inhibited cell growth. This effect was increased 8–12 fold by adding the non-toxic co-enzyme THF. This could be demonstrated in all 3 lines.

Encouraged by the data, we started a prospective randomised clinical trial in which we compared 5-FU monotherapy (600 mg/m$^2$) with the combination treatment (400 mg/m$^2$ THF + 600 mg/m$^2$ 5-FU).

To date 30 patients with hormone-escaped prostatic cancer have been recruited. All suffered from severe pain from bone metastases. The criteria of response were pain remission and time to progression. Side effects were seen in 40%—most of them mild to moderate—predominantly haemotoxicity in the monotherapy group and diarrhoea and stomatitis in the combination arm. These protocols show a remarkable analgesic effect in 27 of 30 patients.

### General Overview with Particular Emphasis on the Role of Prostatic Ultrasound

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Newer, less expensive equipment is making office ultrasound examination of the genitourinary tract practical. In addition, this equipment can be used for vascular flow studies associated with the evaluation of the impotent male and can also be used in conjunction with urodynamic evaluation to image the bladder, bladder neck and proximal urethra. Ultrasound examination performed at the time of an office visit can speed diagnosis and treatment and reduce the cost of patient care.

Applications related to the genitourinary tract include renal ultrasound for the assessment of renal masses, presence or absence of hydronephrosis and perinephric collections. These studies are particularly valuable in the follow-up of patients with urolithiasis, particularly after shock wave lithotripsy to document the presence, absence or resolution of hydronephrosis.

Transabdominal ultrasound of the urinary bladder is used primarily for the assessment of residual urine. Staging of bladder tumours can also be determined with this technology but generally transurethral imaging is superior.

Prostate ultrasound has been used for a variety of indications which include staging of patients with carcinoma of the prostate, assisting in prostate biopsy, assessment of prostate volume and monitoring response to therapy, and the assessment of other benign processes of the prostate and related structures (seminal vesiculitis, prostatitis).

Prostate ultrasound has also been used to assess the seminal vesicles in infertile patients, particularly in those with azoospermia.

Finally, prostate ultrasound is being investigated to determine its role in the screening and early detection of patients with carcinoma of the prostate. This indication remains controversial and unresolved.

## Bladder Cancer

### Flow Cytometry in Bladder Cancer

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Despite a clear improvement in evaluating flow cytometric DNA examinations, present identification rates in bladder cancer are not sufficient as a basis for clinical decisions. Therefore, the aim of our study was to improve the sensitivity and specificity of conventional DNA analysis by means of simultaneous measurement of several tumour cell associated parameters and by additional cell distinction through measuring antigenic determinants of the cellular surface with monoclonal antibodies.

Samples from 206 patients with bladder tumours and from a control group (bladder biopsies, bladder washings and voided urine) were stained with ADB (1,4-diacetoxy-2,3-dicyano-benzene) and PI (propidium iodide) for 5 min at room temperature for simultaneous determination of intracellular esterase activity and cytoplasmatic pH in living cells as well as of DNA in dead cells. In an additional group of 106 ethanol-fixed samples, CEA and Lewis blood group antibodies were used for further cell distinction. Examinations were performed with a 3-parameter flow cytometer (Fluvo-Metricell/HEKA).

Forty percent of the tumour samples showed one or more aneuploid or a tetraploid peak. Adding the analysis of biochemical cell parameters to DNA determination, bladder tumour samples were correctly identified in 83% with a false positive rate of 19%. By evaluation of DNA and cell surface antigens 88% of the tumour samples could be recognised; the rate of false positive results was 21%.

Compared to DNA examination alone, identification rates of bladder tumour cells can be improved by assessment of multiple further cell related biochemical parameters and by additional determination of cell surface antigens in flow cytometry.

## Intravesical Chemotherapy for Ta/T1 Bladder Tumours

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Intravesical chemotherapy is well established as a treatment that reduces the recurrence of Ta/T1 transitional cell carcinoma and doxorubicin, thiotepa, Epodyl and mitomycin C as well as BCG have all been shown to be effective.

The EORTC GU Group has conducted several phase III trials that have compared different drugs, different schedules of treatment and the response of a "marker tumour" with subsequent tumour behaviour. None of these trials has shown the clear superiority of one agent over the others or any definite advantage for immediate post-TUR instillation or the continuation of maintenance instillations for 6 months. EORTC protocols 30831/2 showed a reduction in recurrence rate and tumour rate per year following early doxorubicin treatment plus maintenance instillations compared with delayed treatment and no maintenance therapy. However, an identical trial using mitomycin C revealed no difference for these 2 treatment regimens.

Trials using a marker tumour have failed to recruit, partly because of the complexity of trial design but mainly because of ethical anxieties at the deliberate intention to leave a tumour for observation for 3 months. Preliminary analysis of these aborted trials has shown that 50% of marker tumours have been destroyed by mitomycin C or epirubicin and no tumour has progressed to muscle invasion within 3 months.

The main disadvantage of intravesical chemotherapy is the need for repeated catheterisation, the risk of infection and the increase in chemical cystitis with frequent instillations. Hence 2 MRC trials that used intravesical therapy in a more convenient manner (*i.e.* at the time of initial TUR and at each 3-monthly cystoscopy for 1 year) have been conducted.

Thiotepa failed to show any benefit used in this way compared with TUR alone. The second trial of mitomycin C showed a clearly significant decrease in tumour recurrence when mitomycin was instilled at each cystoscopy, compared either with a single initial instillation or TUR alone.

When several drugs, used in the same way, yield similar results it is important to ask if it is the drugs or the method of treatment that produces the benefit, particularly when there is some evidence that post-TUR irrigation itself may reduce tumour recurrence. This possibility is being investigated.

A variety of prognostic factors influence the recurrence of superficial bladder cancer. Analyses of more than 800 patients in MRC trials has shown that the presence of tumour at the first follow-up cystoscopy, combined with the number of tumours at initial presentation, gives the clearest indication of subsequent recurrence. Single tumours with a clear bladder at 3 months probably need no intravesical chemotherapy and less frequent follow-up. It is encouraging that these results also suggest that poor risk patients, who need effective treatment most, do benefit from the more convenient schedule of mitomycin treatment.

## Survival After Cystectomy (Planned and Salvage) for Transitional Cell Cancer of the Bladder

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We present our experience of treating 41 patients with transitional cell carcinoma of the bladder by either pre-operative radiotherapy and planned cystectomy (22 patients) or salvage cystectomy following local failure of radical radiotherapy (19 patients). Patients were treated between 1983 and 1988 and were followed up until December 1989.

In the group of 22 patients who received pre-operative radiotherapy and planned cystectomy, there was no operative mortality but 2 patients (9%) died within 30 days of operation. At the end of the study 15 patients were alive, 4 had died as a result of bladder cancer and 3 had died from other causes. The 3-year actuarial survival rate following planned cystectomy was 63% (SE = 10%).

Of 130 patients who completed a course of radical radiotherapy, 19 subsequently underwent salvage cystectomy. There was no operative or peri-operative mortality. The time from start of radiotherapy to salvage cystectomy ranged from 4 to 26 months (median 9). At closure of the study 13 patients were alive, 4 had died from bladder cancer and 2 had died from other causes. The 3-year actuarial survival rate following salvage cystectomy was 64% (SE = 14%).

Both cystectomy and salvage cystectomy appear to have acceptably low operative mortality and good survival rates.

## Radical cystectomy and Colo-Caeco Urethroplasty, An Alternative to Ileal Conduit Formation

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The use of "detubularised" intestinal segments enables the creation of high compliant, low pressure reservoirs for bladder replacement. The operation of retrograde cystoprostatectomy also facilitates radical cystoprostatectomy for invasive carcinoma of the bladder (Schegel and Walsh, 1987). The procedure has been performed on 12 patients (10 males and 2 females) between 1986 and 1989.

There have been 3 deaths from metastatic disease. Of 4 initial tubularised segments, 1 was converted to a conduit and a second detubularised using an inlay of ileum; 2 deaths occurred in this group.

Nine detubularised segments were reviewed in 1989. Spontaneous voiding occurred in 6 patients while 3 used self-catheterisation. In 2 men nocturnal incontinence occurred. Urodynamic evaluation revealed a mean volume of 654 ml, a mean filling pressure <20 cm $H_2O$ in all cases, with no unstable contractions during the filling phase. There were 7 cases of metabolic acidosis with respiratory compensation, and 1 case of hyperchloraemia. Two of 4 males are potent post-operatively.

Patients' acceptance of the procedure is high. Colocaeco urethroplasty is an alternative to ileal conduit formation in selected cases.

### Reference

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## Results of Cystectomy, Radiotherapy and Chemotherapy in Invasive Transitional Cell Carcinoma of the Bladder

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We have assessed the results of treatment in 175 consecutive patients treated with curative intent for invasive bladder cancer between 1983 and 1988. Patients had transitional cell carcinoma clinical stages T1–T4 without distant metastases. Treatment consisted of either pre-operative radiotherapy and total cystectomy (35 patients) or radical radiotherapy (140 patients). In the latter group, salvage cystectomy was performed for persistent cancer in 19 patients; 37 patients (about 20% in each group) received neoadjuvant systemic chemotherapy. Data analysis, using logrank tests and Cox regression, revealed that the presence of ureteric obstruction ($P = 0.009$), increasing T stage ($P = 0.035$) and older age ($P = 0.074$) were independent prognostic factors for overall survival (death from any cause), confirming our findings in an earlier series (*Br. J. Urol.* (1989), **63**, 251–258). Comparison of the 2 treatment policies indicated no significant difference in overall survival ($P = 0.52$). Because patients treated under the policy of pre-operative radiotherapy and cystectomy were a prognostically more favourable group, policies were compared after adjusting for prognostic factors; conclusions, however, were unaltered ($P = 0.71$). Patients given chemotherapy survived longer ($P = 0.083$). Since chemotherapy was generally offered to the younger patient ($P = 0.017$) and those with good renal function ($P = 0.11$), its effect on survival was reassessed after adjusting for the above factors ($P = 0.33$). Our data provide no good evidence for the superiority of either treatment policy or for a beneficial effect of chemotherapy.

## Detection of Bladder Cancer in Voided Urine by Monoclonal Antibody BLCA-8

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A new monoclonal antibody, BLCA-8, has been developed by research workers at the Royal Prince Alfred Hospital Urological Cancer Research Unit and the Sydney University to detect exfoliated cancer cells in voided urine. Previously the invasive technique of bladder washings was necessary.

The antibody was developed from bladder cancer cell lines in the laboratory. BLCA-8 is an IgG3 monoclonal which reacts with transitional cell carcinoma (TCC) but not with normal cells or other malignant cells. BLCA-8 reacted with biopsy specimens prepared by immunoperoxidase and immunofluorescence. It was specific against all grades of TCC.

Between 20 and 50 ml of urine were collected, centrifuged, reconstructed and embedded in an equal volume of 1% room temperature agarose. BLCA-8 was added with positive and negative controls. An immunofluorescent antibody was added. The cells were fixed and those showing immunofluorescence were counted as positive. The more malignant the TCC, the more cells appear positive.

BLCA-8 will react with the antigen on the cell for up to 18 h after voiding, making it suitable for clinical use. The technique is more sensitive than urine cytology, is more accurate, easier to perform, does not require expensive equipment and the results can be read by a technician, requiring only counting immunofluorescent cells, and a skilled cytologist is not necessary.

More than 100 urines have been tested with no known false negative results, but there have been false positives. Two patients with haematuria, with previous TCC who were cystoscopically clear, gave positive results and both developed TCC within 5 months, so that the test may have a predictive value.

Future uses may be in patients with low grade TCC and few recurrences in order to reduce the frequency of cystoscopy and to detect upper tract TCC or microhaematuria. The screening of risk groups such as men over 60 who smoke and those exposed to industrial carcinogens and treatment by adding radioactive isotopes might also be considered.

## The Use of Liposomes for Topical Therapy of Bladder Tumours

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Ideally, therapeutic drugs should reach only the diseased sites. Depending on whether the latter are of cellular dimensions or macroscopically large, one can use immunological approaches or rely on physiological or physicochemical methods to achieve this goal. In both cases lipid vesicles, liposomes, are a convenient vehicle for bringing the drugs to the target site, provided they are properly constructed and directed.

The specificity of cellular receptors (such as endolectins) or the characteristic density of the cell surface markers (such as glycoproteins, gangliosides, etc) offers a good starting point for directed drug delivery in the case of microscopically small targets. We have shown that lectins can mediate attachment of the drug-laden liposomes with surface-bound carbohydrate residues to murine bladder tumour cells. In order to bring the drugs into cells, however, lipid vesicles must fuse with the plasma membrane to facilitate drug diffusion into cells. Special choice of the vesicle components and/or drugs is a prerequisite for the success of such approaches.

An alternative, which we are pursuing, is the use of immuno-liposomes which enter the target cells via receptor-dependent endocytosis. In order to escape the intra-lysosomal destruction the carriers are constructed in such a way that they become fusogenic in the acidic intracellular surroundings. Consequently, they can expel the drug from the endosomes into the cytoplasm via fusion with the organelle membrane before being degraded.

Time-consuming liposome optimisation is necessary to ensure high efficiency of the drug delivery into tumours. In this context we are investigating the thermo-regulated and pH-sensitive fusion of the mixed lipid bilayers made from biological and biocompatible lipids. We have found that liposomes composed of dipalmitoylphosphatidylcholine (DPPC) and long chain fatty-alcohols, such as elaidoyl-alcohol, in the stoichiometric molar ratio 1:2, fuse at temperatures about 42°C. Mixtures of DPPC and elaidic acid (EA) in the same molar ratio also fuse at slightly elevated temperatures but their fusion rate is faster by a factor of more than 10 and more efficient in the acidic surroundings (relative fusion rate at pH 4.9: 24 min) than in the neutral pH region (relative fusion rate of pH 7.3: 3.75 min). If DPPC is replaced by dipentadecanoylphosphatidylcholine and pH-dependent, fusion is maximal at 37°C.

By using liposomes of the types described, in combination with localised (ultrasound-induced) hyperthermia, we have achieved a 50% increase of the local liposome concentration in the heated body site as compared to the non-heated tissue.

## Systemic Chemotherapy for T3 Bladder Cancer

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For most urologists and oncologists systemic chemotherapy has been regarded as a treatment for metastases, either as treatment for disseminated tumour or as adjuvant treatment for undetectable micrometastases in patients undergoing cystectomy or radiotherapy in the hope of cure. No trial of single agent adjuvant chemotherapy has yet demonstrated any survival benefit for locally advanced bladder cancer. However, the MVAC combination has now been shown to be more effective than cisplatin alone in metastatic disease and phase II trials suggest that other cisplatic-containing combinations such as CMV are as good as MVAC. For this reason, many patients are being given adjuvant chemotherapy with such combinations but it is vital that the benefit of this practice is proved by clinical trials. To this end, 2 randomised trials are being conducted in T2, T3 and T4a transitional cell carcinoma.

The SWOG trial 8710 compares cystectomy plus 3 cycles of MVAC with cystectomy alone. The MRC/

EORTC intercontinental trial compares 3 cycles of CMV prior to cystectomy or radiotherapy with the same definitive treatment without chemotherapy. Both of these trials need to be completed rapidly and the participation of all urologists is recommended.

In the hope of improving the quality of life of patients with locally advanced bladder cancer by avoiding cystectomy, we have investigated the role of chemotherapy in the initial treatment of primary T3 bladder tumours. In Newcastle, 30% of all patients with T3/T4 tumours treated initially with cisplatin-containing chemotherapy have achieved complete response after 4 cycles of treatment. These patients have not undergone cystectomy or radiotherapy and have received only 1 or 2 more cycles of the same chemotherapy. Of 25 such patients, 21 remain alive and disease-free 10 to 48 months following chemotherapy.

It is probably expecting too much of chemotherapy (or radiotherapy) to destroy bulky tumours in their entirety and preliminary "debulking" by TUR is logical. Thus the concept of combining thorough endoscopic resection with chemotherapy has been developed. To date, 34 patients with T2/T3 transitional cell carcinoma have been treated by radical TUR plus 3 to 5 cycles of cisplatin 70 mg/m$^2$ and methotrexate 40 mg/m$^2$. All patients have been evaluated and followed up by 3-monthly cystoscopies and resection biopsies. After 1 year, 25 of 31 are free of invasive disease, as are 11 of 15 after 3 years. The relative contribution of chemotherapy and the extent of the TUR is not clear and this requires further study.

In both of these studies, if chemotherapy has failed, radiotherapy or cystectomy has been used without additional complication.

The toxicity of present-day chemotherapy should not be under-estimated, or the efficacy of neoadjuvant chemotherapy over-estimated, but the use of primary cisplatin-containing chemotherapy to achieve bladder preservation or increase survival is worthy of further investigation.

## Tips for Endoscopic Technique in Bladder Tumours

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Many urologists fail to appreciate that the endoscopic treatment of bladder cancer requires operative techniques that are different from those employed in resecting the prostate.

The first requirement is proper equipment, which must include a continuous flow resectoscope sheath with low pressure suction of the effluent balancing the inflow of isotonic irrigation fluid. Only by this means can the extent of bladder distension be controlled and the resection of tumours on the anterior wall and dome facilitated. Also, a full selection of electrodes is essential, including a bladder wall loop (bent to 30° rather than the usual 90°), a knife or bee-sting incising electrode and a roller ball for use with cutting diathermy to destroy patches of carcinoma *in situ* or small tumours, instead of fulguration with the coagulation current.

Resection of tumours on the posterior, anterior walls and dome is best done with the bladder wall loop, swinging the whole resectoscope with the loop extended through an arc that follows the contours of the bladder wall in a movement that is entirely different from that used for the 90° loop.

Obturator spasm causing full thickness bladder perforation is a recurring problem. Reducing the strength of the diathermy current and giving intravenous muscle-relaxing drugs can help, but the anxiety of post-operative extravasation remains. The simple solution is to complete the tumour resection and deliberately enlarge the perforation so that any extravasated fluid can drain back into the bladder.

Tumour treatment sometimes causes fibrosis of ureteric orifices and subsequent hydronephrosis. The usual remedy is reimplantation of the ureter but this can be avoided by resecting the scar tissue combined with an extended meatotomy. The difficulty is locating the ureter from within the bladder, but this can be accomplished easily by placing a guidewire down the ureter by pre-operative percutaneous puncture and resecting on to the guidewire tip using X-ray fluoroscopy.

The technique for the intramural resection of the lower ureter as the first stage of nephroureterectomy has been described elsewhere, but anxiety has been expressed that this may cause extravesical tumour recurrence. Provided meticulous attention is paid to endoscopic technique we have not found this to be a problem. Maintaining low intravesical pressure, the ureter is disconnected completely from the bladder wall and its end sealed thoroughly by coagulation diathermy in the perivesical fat, followed by its removal from the pelvis before proceeding with dissection of the kidney.

Complete endoscopic resection of muscle-invasive bladder tumours has been practised by some urologists for many years, either as a 1- or 2-stage procedure. These full thickness resections of the bladder wall require patience, meticulous haemostasis and post-operative catheterisation for 5 to 10 days.

## Bladder Advancement Extension Graft Technique

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The Boari flap and psoas hitch are well established manoeuvres for overcoming deficiencies in the lower ureter. Their effectiveness in upper ureteric defects is limited. In such cases it is important to determine how far proximally the bladder can be mobilised without tension or jeopardising blood supply. Alternatively, renal autotransplantation, ileal interposition or nephrectomy may be performed, though these approaches are less attractive options with well recognised disadvantages.

Based on previous experience with partial thickness bladder grafts, a study was designed to investigate the role of omentally supported autologous, partial thickness bladder grafts as cranial extensions from Boari flaps, as 1-stage procedures. The concept was to extend urothelium in continuity so that a ureter could be replaced completely and simply by a graft which, with the Boari flap, formed a bladder horn extending to the renal pelvis. In addition, a separate tongue of omentum was fixed in a gutter of bladder wall so that this would ensure viability for an island patch retrieval graft on this omental pedicle, should it be required to correct any area of stenosis which might develop subsequently.

Ten dogs were studied for 6 months from their initial procedures. At the end of the study, none of the upper tracts on the operated sides was obstructed, although 2 dogs required pedicle retrieval grafts for stenoses at the upper graft/ureter anastomosis sites at 11 and 16 weeks respectively. Histologically, healthy urothelium was seen with an abundance of viable muscle in graft walls supported by omentum.

This study has demonstrated that the technique promises to complement Boari flap and psoas hitch procedures when these are insufficient to accommodate a ureteric deficiency by themselves with a high likelihood of success.

### Does DNA Ploidy Enhance TFR Predictability of Recurrences in Superficial Bladder Cancer?

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We have examined a number of parameters in superficial bladder cancer with respect to their ability to indicate the likelihood of recurrence. Our studies have demonstrated that transferrin receptor (TFR) expression in the primary, an indicator of cellular proliferative activity, is most predictive in this regard (*Br. J. Urol.* (1990), **65**, 339–344). Since a number of markers may be more predictive than any one marker alone, we examined DNA ploidy of the primary tumour with a view to adding this to TFR status in a tumour profile.

A total of 71 patients, whose original tumours were superficial and characterised for their TFR status, were followed up for 2 years. Of 46 TFR+ tumour patients, 72% had recurrences compared with 10/25 TFR− tumour patients, the difference being significant ($P<0.05$ with Yeates correction). Of these primary tumours 58 were also examined for DNA ploidy, with 14/20 (70%) aneuploid and 22/38 (58%) diploid being followed by recurrences; 13/17 (76%) aneuploid and TFR+ tumours were followed by recurrence compared with 5/12 (42.5%) diploid with TFR− status, the difference not being significant. The addition of abnormal cytology to TFR+ status was associated with a significant difference from TFR− tumours with normal cytology with respect to recurrence formation but not in combination with DNA ploidy.

Thus DNA ploidy did not complement TFR status with respect to prediction of recurrences in the first 2 years of follow-up and is no longer included in our tumour profile.

## Other Tumours

### Primary Retroperitoneal Lymphadenectomy vs Surveillance for Early Stage Testis Cancer

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Surveillance of patients with early stage non-seminomatous germ cell tumours involves frequent, regular and prolonged follow-up which includes physical examination, chest X-ray, tumour markers and CT scans. This requires guaranteed review at a centre with these facilities and is associated with a variable degree of anxiety for the patients. Relapse occurs in 30% of patients, mostly within the first year, half of this progression being distant metastases and half being detectable retroperitoneal node deposits, although it is reasonable to assume that the majority will have microscopic nodal disease. A minimum of 4 cycles of chemotherapy are required to treat relapsing patients at this stage. If surveillance is less thorough, relapse may not be detected until a late stage, at which time more chemotherapy may be required and surgery may be needed for some patients.

Routine primary retroperitoneal lymphadenectomy has been standard management of early stage testis teratoma in several countries. Although a major operation, there should be no mortality and little serious morbidity, but most patients have no ejaculate postoperatively and this has been an important disadvantage. The recent modification of the surgical technique by Donoghue as a nerve-sparing procedure avoids this complication without apparently reducing its efficacy.

Microscopic nodal metastases are found in 30% and to avoid the need for intensive follow-up, these patients are now given 2 cycles of "prophylactic" chemotherapy. Thereafter, examination, chest X-ray and tumour markers may be checked at a non-specialist centre less frequently and the chance of relapse is very low.

At the present time the results of both strategies are the same: virtually 100% cure. Other factors being equal, the choice between the 2 treatment policies may therefore be a personal one for the patient rather than his doctors to decide

On the one hand, unnecessary surgery is avoided but there is a 30% chance of needing extra cycles of chemotherapy and the need for rigorous follow-up at a specialist hospital. On the other hand, after primary lymphadenectomy, the patient is reassured that all desirable definitive treatment has been undertaken and follow-up is a matter of routine, although the cost is a small increased risk of infertility.

If a regular surveillance is difficult or the patient likely to default, primary surgery is preferable. However, this should be performed by a surgeon with regular experience of the procedure to maximise its nerve-sparing potential. Frozen sections of all nodes should be examined during surgery and if positive, the nerve-sparing technique should be abandoned in favour of the unilateral or bilateral conventional dissection.

## Testicular Cancer

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Patients with testicular tumours typically appear with pain and/or a scrotal mass. These tumours are an important cause of cancer deaths in men between 30 and 40 years of age. Most testicular cancers arise from germinal cells, those cells which have retained the capacity for undifferentiated growth from early development. Many show a mixed histology including 2 or more of these types. Only 10% of these tumours are non-germinal in origin and are known as epithelial tumours. The identification of serum markers has helped in the evaluation of testicular tumours. Alpha fetoprotein is elevated in approximately 70% of patients with embryonal cell carcinoma and 75% of patients with yolk sac tumour. It may be absent in patients with choriococarcinoma and pure seminoma. The level of hCG is elevated in all patients with choriocarcinoma and 60% of those with embryonal cell carcinoma, 25% of patients with yolk sac tumours and less than 10% of patients with pure seminoma.

Much controversy relates to the treatment of patients with clinical stage A or absence of evidence of retroperitoneal nodal disease. Traditionally retroperitoneal lymph node dissection is performed and chemotherapy administered to those patients with positive nodes. Protocols of surveillance are relatively new but relapse rates have varied from 17 to 40%. When relapse is detected (usually in the retroperitoneum), chemotherapy is then administered.

Salvage rates between the 2 approaches appear comparable but controversy continues. For patients with detectable metastatic disease chemotherapy with cisplatin-based chemotherapy has been most successful. Additional chemotherapy, including VP 16 (etoposide and ifosfamide), have proven to be of value in patients not responding to this approach.

Most agree that if nodal disease persists following chemotherapy, then retroperitoneal lymph node dissection is needed to define the histological characteristics of the remaining tissue.

## Retroperitoneal Lymph Node Dissection Following Chemotherapy for Advanced Testis Cancer

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Retroperitoneal lymphadenectomy for residual para-aortic nodal metastases after previous chemotherapy should be performed by a surgeon who is prepared to undertake these extensive and sometimes difficult dissections on a regular basis. Patients are selected for surgery if there is an incomplete clinical response judged by CT scan or persistently elevated tumour markers 2 months after completion of chemotherapy. Patients with enlargement of para-aortic nodes following chemotherapy should not be dismissed, provided there is evidence of response elsewhere, as enlargement may be due to tumour necrosis or cystic change, which indicates a favourable prognosis following surgery.

Opinions differ concerning the extent of the dissection that should be performed. Initially, the procedure was often no more than a "de-bulking" removal of palpable tumour mass but it is now accepted that meticulous dissection from the renal hilum to the sacral promontory should be completed, with extension to the ipsilateral internal inguinal ring in all patients and above the renal vessels (and above the diaphragm) if indicated. Bowel resection, nephrectomy, ureteric reconstruction and resection and reconstruction of the great vessels are sometimes required. Post-operative ejaculatory failure is usual but prolonged hospital stay and serious morbidity are uncommon.

Histological examination of the operative specimen usually shows necrotic tissue only in 30%, mature teratoma in 50% and malignant tissue in 20%. The proportion of patients with persisting cancer may not seem to justify such extensive surgery but the identification of these poor risk patients is essential as 70% can be salvaged by additional poly-chemotherapy.

The distinction between immature teratoma and malignant tissue is also important because the former appears to have a good prognosis and, like maturing teratoma, thorough surgical excision is all that is required.

### Gene Expression of Transforming Growth Factor in Human Renal Carcinomas

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The uncontrolled growth of tumour cells may be due in part to the ability of transformed cells to elaborate a spectrum of different polypeptide growth factors that may be involved in the autocrine stimulation of these cells. Two major classes of transforming growth factors have been identified, purified and cloned, TGF− and TGF −B. Since the cDNA for TGF− was originally isolated from a renal carcinoma cell line, we decided to study human renal carcinomas for the expression of m-RNA coding for TGF− using the Northern blotting technique.

Tumour tissue was obtained by nephrectomy and frozen in liquid nitrogen until use. RNA was extracted by the guanidinium/cesium chloride method. All renal carcinomas were found to express a specific 4.8 kb TGF− m-RNA. Moreover, in some carcinomas an additional TGF− transcript of 2.3–2.5 kb length was identified. The hybridisation signal of both RNA species was strong enough to be detected even on the blots with total RNA. For comparison, adjacent normal tissue from the same kidney was tested for TGF− expression.

Although the gene was also expressed in normal renal tissue, the degree of expression was much lower than in transformed regions of the kidney.

Quantitative and qualitative differences in TGF− expression may therefore contribute to the clinical heterogeneity of human renal carcinoma.

### Adenocarcinoma in Solitary or Both Kidneys: Surgical Management

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A total of 18 patients underwent partial nephrectomy for presumed adenocarcinoma, having presented with a solid lesion in one or both kidneys. In 4 the lesion was in the middle third of the kidney. In 3 cases the excised lesion was found to be benign. During the last 12 months the Nd:YAG laser scalpel has been used for partial nephrectomy, providing greater ease of haemostasis. Adequate clearance of the tumour was confirmed, this sometimes necessitating frozen section.

Adenocarcinoma in a solitary kidney or both kidneys may force an attempt at partial nephrectomy in circumstances that are less than ideal because of tumour location and size. Partial nephrectomy may be performed for all polar renal tumours, regardless of size, and for all small or peripheral renal tumours, instead of total nephrectomy. Even tumours in the mid zone are resectable and compatible with long-term survival. The use of the Nd:YAG laser has facilitated haemostasis in these more difficult cases.

## Miscellaneous

### Sperm Aspiration and Fertilisation *in vitro* in the Treatment of Obstructive Azoospermia

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Ductal obstruction is a common cause of sterility in men and responds poorly to surgical treatment. We present our experience of sperm aspiration, fertilisation *in vitro* and embryo replacement in the treatment of this condition.

Eleven patients with obstructive azoospermia underwent this treatment; 2 were treated 3 times, resulting in a total of 15 attempts. Of these 11 patients, 4 were sterile due to a previous vasectomy, 3 of them having undergone several attempts at reversal in the past. A further 3 men had idiopathic subcapital epididymal obstruction and 2 more had bilateral congenital absence of the vasa deferentia. In all patients, except those who had undergone vasectomy, the site of the obstruction had been confirmed by scrotal exploration.

Superovulation in the female partner was induced using a Leuprolide/hMG pituitary down regulation regimen. On the day of egg aspiration, sperm were aspirated from the epididymis under general anaesthesia from a point proximal to the site of the obstruction. The sperm were aspirated into medium containing 10% inactivated human serum. After washing and treatment of the sperm with a 1% solution of the sperm motility stimulant, pentoxifylline, after which a proportion of the aspirated sperm were passed down a discontinuous Percoll gradient, the sperm were then used for egg insemination. The numbers of sperm that were aspirated varied from 0–20 million and the grade of movement also varied greatly. Although the fertilisation rate was poor, fertilisation was achieved in 6 of the 15 attempts.

The embryos so obtained were replaced into the fallopian tubes or the uterus of 6 of the consorts using the technique known as tubal embryo stage transfer ("TEST"). For the remaining woman, a uterine transfer was carried out as tubal blockage was present. From the 6 embryo transfers 2 pregnancies were achieved, 1 using sperm from a man with an obstruction due to vasectomy and the other from a man with idiopathic upper epididymal obstruction.

It has thus been demonstrated that it is possible to achieve pregnancies using these techniques and that fertilisation can occur using spermatozoa taken from the caput epididymis.

## Animal Models for Epididymo-Epididymostomy: Developing an Alternative Microsurgical Procedure for Vaso-Epididymostomy

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The present success rate for high level microsurgical vaso-epididymostomy in patients with obstructive azoospermia is still poor in comparison with more distal vaso-epididymal bypasses, suggesting that development of a successful method of preserving the maturation and storage functions of the epididymis might increase the fertility success rate.

We have developed a segmental bypass of the distal caput-proximal corpus regions of the epididymis in the rat. In this procedure epididymides in 11 adult male Sprague-Dawley rats were exposed through a scrotal incision and a convolution of the duct was attached to an opened convolution in the mid-caput region using a standard microsurgical technique. Each male was left for at least 3 months after the microsurgical bypass operation to allow sperm clearance from the caudal storage region. Six of the 11 rats were proven fertile after surgery by siring litters from mating trials up to 12 months later. Patency of the anastomoses was confirmed in 3 animals by laparotomy and recovery of large numbers of sperm with normal motility from cauda epididymis distal to the anastomosis site and also from the vas. Similar surgery in an adult male rabbit resulted in normal post-operative semen profiles and an *in vivo* fertilisation rate of 100% from one mating trial 8 months after surgery.

In conclusion, we now have a reliable animal model which can be used as an experimental tool in studying the function of the epididymis and may be an alternative to vaso-epididymostomy in selected patients.

## Results of a Technique of Rejoining the Vas Deferens After Vasectomy

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A single layer vas anastomosis over a 3/0 nylon stent, using 8/0 monofilament nylon suture and an operating microscope, has been used. Care is taken not to penetrate the lumen of the vas deferens with the sutures. The stent is removed the day after operation and the patient discharged from hospital then, with light exercise only advised for 1 week.

Of 83 operations performed, 68 patients were evaluable by semen profile and/or achievement of a pregnancy, or vasography; 63 anastomoses were patent (93%) after the first operation, 4 (6%) were obstructed, and 1 patient with azoospermia refused vasography.

The operation was repeated in all 4 who were obstructed and 3 now have sperm in the semen. The fourth had a TURP by a colleague 8 weeks after the operation and subsequently has had no ejaculate. Of the 49 patients with sperm in the semen, 30 replied to a letter of enquiry regarding pregnancy. Seventeen had achieved at least 1 pregnancy and 13 had not.

This is a relatively simple technique with minimal complications, low morbidity and a high success rate. Re-operation by the same technique on those who were found to be obstructed after the first operation had a high success rate.

## Aids and Hepatitis B and C—Contamination Risk at Transurethral Resection

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Human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) are all transmitted by minute amounts of infected blood. Surgeons are at risk through a number of routes, including blood splashes to the mucous membranes of eyes, nose and mouth, needle stick injuries and blood spillage on chapped ungloved hands. The endoscopic surgeon is unaware of nearly all facial contamination because the splashes are frequently both minute and dilute. Sodium fluorescein, an indelible dye detectable in dilutions of 1–2 parts per million, has been used in this prospective study as a marker for TUR irrigating fluid. In 17 of 20 consecutive operations its presence on the face of the operator was obvious, even though only a few splashes were visible to the naked eye. There was a random distribution of splashes and also a recurring pattern of contamination of the orbit of the operating eye and the tip of the nose. Vaccination against hepatitis B is recommended for all endoscopic surgeons, together with the use of protective glasses and a mask that covers both the nose and mouth. The greatest danger to the health care team is from an infectious patient who is an unknown risk.

## The Role of Statistics and Clinical Trials in Urology

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Urology has developed as a clinical, surgical specialty with little conception of the need for clinical trials to demonstrate the efficacy of different surgical procedures.

Review of 20 publications reporting the results of treatment for various urological problems, taken at random from recent urological journals, reveals that only 1 was a randomised study with sufficient patients to show a valid conclusion. Two other randomised studies were reported with inadequate patient numbers, 12 others were uncontrolled retrospective reviews and the remaining 5, although conducted prospectively, did not yield statistical data adequate to support the conclusions of the authors.

Participation in a randomised trial implies that the doctor does not know which is the best treatment and the confidence of some doctors as well as patients is upset by this uncertainty. Nonetheless, in the changing climate of urological practice there is a growing need to be certain of the relevant merits of different treatments, particularly as several forms of therapy are now available for many urological disorders.

Some new treatments are so obviously effective that a trial is not needed to demonstrate their benefits. However, this is unusual and the differences between competing treatments are often smaller than suggested by initial experiment, clinical impressions and promotional advertising. Unfortunately, small differences, no matter how worthwhile, require large numbers of patients to be proven with an acceptable degree of certainty. To conclude that "there is no difference" may require even more. For this reason, few clinical questions can be answered by single-institution studies.

Randomised multi-centre trials are difficult to organise and prone to failure but they should probably become a routine part of a urologist's work in the future.

## Critical Evaluation of Vesicourethral Reflexes and their Neuropharmacological Basis in Non-Human Primates

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In the human the precise mechanism of vesicourethral integration remains obscure because neuropathy usually produces mixed or incomplete loss of neural function. Experimental studies in non-human primates (Macaca nemestrina) have shown remarkable similarities to the human female in respect of the functional innervation of the bladder and urethra.

Dual microtip studies of the vesicourethral reflexes have been conducted. The neurotransmitters involved in the co-ordination of vesicourethral function have been evaluated with respect to the cholinergic and adrenergic systems.

A comparison of the vesicourethral pressure relationships between the monkey and the human demonstrated considerable variability of response in the monkey without obvious causation.

Investigation of this phenomenon has not implicated urethral over-distension. The possibility that ketamine anaesthetic may be responsible appears unlikely in view of our previous experience using different cystometry techniques.

We have been unable to demonstrate a reproducible role for beta adrenergic receptors in the modulation of the urethral relaxation prior to the initiation of reflex voiding.

## Use of Ultrasound in Penile Disorders

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As a surface organ, the penis is readily accessible to ultrasound, using a water-filled cushion and a variety of ultrasound probes. It may be used in assessment of the size and depth of the plaques in Peyronie's disease, allowing more objective follow-up of this condition.

In acute penile rupture, ultrasound can show the size of the defect and also assess the size and depth of any subsequent scar.

The corporal arteries can be clearly shown in patients with erectile impotence, and pre- and post-papaverine assessments performed to assess the increase in blood flow and diameter of the artery. This is particularly useful using colour-flow Doppler and duplex scanning.

A number of other miscellaneous conditions have been shown, including thrombophlebitis of the dorsal penile vein and para-urethral sterile abscess.

In patients who have suffered previous priapism, ultrasound can clearly show the extent of corporal fibrosis as a guide to the prognosis of recovery of erections and of any difficulties which may be experienced with insertion of a penile prosthesis.

## The Continence Foundation of Australia

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Over the last 3 years multidisciplinary groups of health professionals interested in incontinence have co-operated in establishing Continence Promotion Groups in each of the states. These groups have comprised urologists, gynaecologists, geriatricians, manufacturers, nurses, physiotherapists, occupational therapists, sufferers and their carers. At the First National Conference on Incontinence in Melbourne in 1987 it was decided to form a national body to co-ordinate the efforts of the groups in the states into a more effective and efficient organisation.

The Continence Foundation of Australia was launched on 3 November 1989 at the Second National Conference on Incontinence in Sydney. The aims of the Foundation include improvement in the training of services to the incontinent, improvement in the training of doctors and other health professionals in the treatment of incontinence, improved public awareness and the promotion of research by the establishment of a research fund. Continence promotion activities in the print and electronic media have already raised the level of public awareness of the problem amongst the community and special interest and advocacy groups.

State and federal government support has already been forthcoming to fund the secretariat of foundation, educational projects and continence promotion activities. Many of the objectives will have an impact on the urologist and other specialists who deal with incontinence.

## Use of Magnetic Resonance Imaging (MRI) in the Assessment of Prostatic Mass

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MRI scanning was used to assess the size of prostatic tissue in patients undergoing elective transurethral prostatic resection (TURP). From these measurements, mass calculations of resected tissue were determined. The relationship between this and actual resected tissue mass was sought.

The patient group consisted of 10 men, mean age 70 years (range 57–77), undergoing elective TURP. MRI scanning was performed up to 3 weeks prior to surgery and again 6 to 8 weeks post-operatively. At operation, the excised prostatic tissue was weighed on electronic scales. MRI measurements were made by a independent observer. Data were analysed by regression analysis.

A significant correlation ($P<0.01$) was found when the preoperative MRI mass minus the post-operative MRI mass (calculated mass resected) was compared with the actual resected prostatic mass weighed at time of surgery. Furthermore, there was a highly significant ($P<0.001$) constant correlation between the pre-operative prostatic mass and the amount of prostatic tissue resected: in this study, the mean proportion of prostatic tissue resected was 41%.

It is concluded that MRI scanning is a valid method of assessing prostatic mass. The proportion of prostatic tissue resected by the transurethral method does not change significantly with different prostate mass.

## What do General Practitioners know about Incontinence?

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There is a tendency for specialists to assume that a certain level of competence exists in their general practitioner colleagues in relation to their particular specialty. In the field of incontinence management it has become apparent that certain deficiencies of knowledge might exist in the community which may require addressing by post-graduate education programmes. A survey of 100 randomly selected general practitioners was undertaken in order to ascertain their level of knowledge and expertise about incontinence.

Only 15% of GPs acknowledged that they did not know the difference between stress and urge incontinence. However, of the 85% who thought they knew the difference only 20% could accurately define both urge and stress incontinence; the majority confused stress with urge.

In the treatment of incontinence most GPs had heard of drug therapy. The most commonly prescribed drug was imipramine for both stress and urge incontinence quite indiscriminately.

Anticholinergic agents were popular without distinction being made for the type of incontinence being treated. Prazosin was mentioned as a treatment of stress incontinence and Urecholine was used to treat urge incontinence. There was considerable confusion about the place of other conservative therapy.

The responses indicated a widespread ignorance of the proper assessment and management of incontinence by GPs. Women practitioners tended to be better informed than males but there was little correlation with year of graduation.

These findings suggest that there is a need for us to educate our general practitioner colleagues to dispel their ignorance and to encourage them to work more closely with urologists to help their incontinent patients. There is clearly a need for us to take more care in educating our medical students in the management of incontinence rather than leaving this up to tutors from other specialties.

## The Urologist's Approach to Vesicovaginal Fistula

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Vesicovaginal fistula is uncommon in western countries. The majority follow hysterectomy or radiotherapy. The average urologist will see few cases. A personal experience with abdominal closure in 51 consecutive patients over a period of 23 years has been analysed.

In 9 cases a combined transvesical-vaginal exposure was used. Of these 2 recurred and were later closed vaginally. Because of these failures, a transperitoneal operation, as advocated by O'Connor, was adopted in the remaining 41 patients, with 1 failure in a radiation fistula. The transperitoneal operation is recommended. By splitting the bladder into the fistula, a wide exposure is obtained and the omentum can be interposed between bladder and vagina.

This operation is suitable for all vesicovaginal fistulae. Unlike the vaginal operation, it requires no special surgical expertise and has a success rate near 100% in non-irradiated patients.

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# Effect of Clean Intermittent Catheterisation on Radiological Appearance of the Upper Urinary Tract in Children with Myelomeningocele

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Summary—Of the 102 consecutive children with myelomeningocele who were treated by intermittent catheterisation between 1977 and 1985, 89 were investigated with regard to the development of the upper urinary tract. The median follow-up period was 6.7 years. Dilatation and vesicoureteric reflux were assessed by means of repeated urography and voiding cystourethrography. Of the 49 children with normal radiology at the start of catheterisation, all but 2 remained normal. In 27 with isolated dilatation of the upper urinary tract or reflux at the start, 17 subsequently became normal. Dilatation together with reflux was seen in 13 patients at the start; 3 became normal, 4 still had reflux and in 6 patients both dilatation and reflux persisted. Intermittent catheterisation thus had a positive effect on the upper urinary tract in the vast majority of cases. In children with both dilatation and reflux, however, there is a risk of deterioration and they should be followed up closely.

After the introduction of clean intermittent catheterisation (CIC) by Lapides and Diokno (1972), this rapidly became the treatment of choice in neurogenic bladder dysfunction (Kaplan and Firlit, 1983). CIC has been reported to improve dilatation of the upper urinary tract and vesicoureteric reflux and to diminish incontinence and urinary tract infection (Kass *et al.*, 1981; Scott and Deegan, 1982; Barbalias *et al.*, 1983; Brem *et al.*, 1987). However, patients in the study groups have often been selected and have included both children and adults. Furthermore, no detailed analysis of the development of changes in the urinary tract has been undertaken.

The present study describes an unselected series of children with myelomeningocele who began CIC between 1977 and 1985. The development of the urinary tract was monitored by repeated radiological investigations in order to examine the effect of CIC on the urinary tract.

## Patients and Methods

All patients with myelomeningocele born in the western region of Sweden are cared for at the Children's Hospital, Gothenburg, during the first year of life. They are then referred to Bräcke Östergård, the rehabilitation centre for the region with a total population of approximately 2 million. A team which includes registered nurses specially trained in urotherapy, paediatric urologists and paediatric nephrologists, is responsible for the urological management of these children. A standard protocol is used as a basis for follow-up, in addition to which every child has an individual plan. Acute problems, *e.g.* urinary tract infections, are dealt with by the local rehabilitation organisations in each of the 7 counties comprising the western region.

CIC was introduced in Gothenburg in 1977. By April 1985 a total of 102 children with myelomeningocele had commenced CIC; 6 of these were not fully followed up and have not been included in the evaluation. A further 7 were excluded because they had undergone urological surgery less than 6 months

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before the start of CIC. Of the remaining 89 patients (51 girls and 38 boys), the median age at the start was 6 years (range 0.1–18) (Table 1).

All patients had bladder voiding difficulties with varying amounts of residual urine. Either abdominal straining or manual compression was used to empty the bladder in all except 10 of the children below 6 months of age. All were incontinent and needed nappies. However, the main indication for CIC was medical in 40 patients: dilatation of the upper tract (11), reflux (16), or dilatation combined with reflux (13).

Catheterisation was difficult in 3 boys because of sphincter contracture. They were given perineal urethrostomies, 2 within 2 weeks of the start of CIC and 1 after 10 months, which greatly facilitated catheterisation.

In December 1988, 87 patients were still using CIC. One boy stopped because of continuing incontinence after failure of an artificial sphincter operation, and 1 girl died from cerebral complications 4.5 years after the start of CIC. Three children (13.6–16.8 years of age) interrupted CIC for 1 to 2 years but recommenced because of deterioration of the upper urinary tract. At the end of the 1988, the total CIC time of the 89 patients was 592 years (range 1.1–10.7; median 6.7).

Urography (Claesson *et al.*, 1981) and voiding cystourethrography (VCU) (International Reflux Study in Children, 1985) were performed according to standard techniques immediately before the start of CIC and then at intervals of 1 to 3 years, but usually every 2 years. The median number of urographies after the start of CIC was 3 (range 1–10) with the most recent after a median of 5.3 years (range 1.1–10.9). The median number of follow-up VCUs was 2 (range 1–7) and the most recent was performed after a median of 4.6 years (range 1.0–9.2). Patients who had anti-reflux procedures were included in the study until the time of surgery.

**Table 1** Age at the Start of Catheterisation

| Age (years) | Patients included in study | Excluded patients | |
|---|---|---|---|
| | | *Inadequate follow-up* | *Urological surgery* |
| <0.5 | 10 | 0 | 0 |
| 0.5–<1 | 7 | 0 | 0 |
| 1–<4 | 16 | 2 | 1 |
| 4–<7 | 15 | 0 | 0 |
| 7–<12 | 24 | 1 | 3 |
| ≥12 | 17 | 3 | 3 |
| Total | 89 | 6 | 7 |

The sequence of radiological films from each patient was evaluated according to a standard protocol, with particular emphasis on changes between investigations. Dilatation of the upper urinary tract was evaluated on urographic films without abdominal compression and was registered separately for calices, pelvis and ureter as being slight (grade 1), moderate (grade 2) or severe (grade 3). Renal scarring was defined as caliceal deformity with thinning of the corresponding parenchyma (Hodson and Wilson, 1965). Reflux on VCU was assessed according to a 5-point scale (International Reflux Study in Children, 1985). In the evaluation, each child was represented by the renal unit with the most severe abnormality, and for dilatation the most marked grade for either calices, pelves or ureters was used.

## Results

Patients were divided into groups according to radiological status at the start of CIC, *i.e.* no reflux and no dilatation of the upper tract (49), isolated dilatation (11), reflux without dilatation (16) and reflux combined with dilatation of the upper tract (13). During treatment the number of patients with reflux as well as dilatation diminished. At evaluation, the number with isolated reflux had decreased from 16 to 6 and isolated dilatation from 11 to 8. Complete normalisation was seen in 20 of the 40 patients with reflux and/or dilatation at the start of CIC. Four patients acquired upper tract dilatation. The change within the groups is seen in Table 2.

Figures 1 to 3 give a more detailed description of the X-ray findings and also illustrate the change in grade of abnormality. In addition to the 11 patients with dilatation but no reflux at the start of CIC, 2 previously normal children had acquired isolated slight dilatation at the evaluation (Fig. 1). Improvement was seen in 7, of whom 5 became normal.

**Table 2** Status of Patients with Reflux and Dilatation before and after CIC

| *Status at start of CIC* | | *Status at evaluation* | | | |
|---|---|---|---|---|---|
| | | *R−D−* | *R−D+* | *R+D−* | *R+D+* |
| R−D− | 49 | 47 | 2 | 0 | 0 |
| R−D+ | 11 | 5 | 6 | 0 | 0 |
| R+D− | 16 | 12 | 0 | 2 | 2 |
| R+D+ | 13 | 3 | 0 | 4 | 6 |
| Total | 89 | 67 | 8 | 6 | 8 |

R = reflux, D = dilatation, − = absent; + = present.

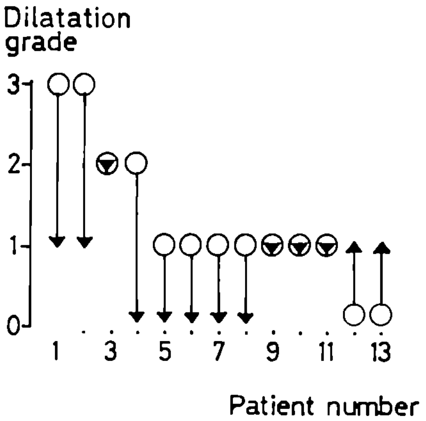

**Fig. 1** Changes in dilatation in 13 patients (11 with isolated dilatation at the start of CIC and 2 acquiring dilatation). None had reflux at any time Each child is represented by the most marked grade of dilatation of calices, pelves or ureters on either side ○ = status at the start, ▲ = status at evaluation; ⊙ = no change

The X-ray changes in 14 of the patients with isolated reflux at the start is shown in Figure 2. Reflux disappeared in 12, improved in 1 and was unchanged in 1. No previously normal individual acquired reflux.

Figure 3 shows the X-ray findings in children with combined dilatation and reflux at the start or at evaluation. Of the 13 children with such findings at the start, dilatation disappeared in 7, improved in 3, was unchanged in 2 and increased in 1. Reflux disappeared in 3, improved in 5, was unchanged in 2 and increased in 3. Two children with isolated reflux at the start developed grade 1 dilatation; reflux was unchanged in 1 and increased in 1.

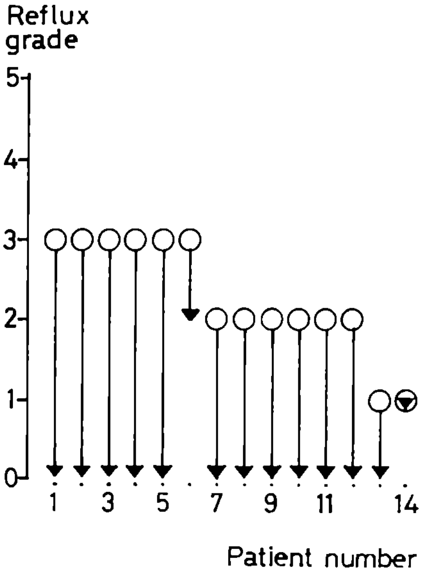

**Fig. 2** Changes in reflux in 14 patients with isolated reflux at the start of CIC or evaluation and no dilatation at any time. Each child is represented by the renal unit with the most severe reflux. Symbols as in Figure 1.

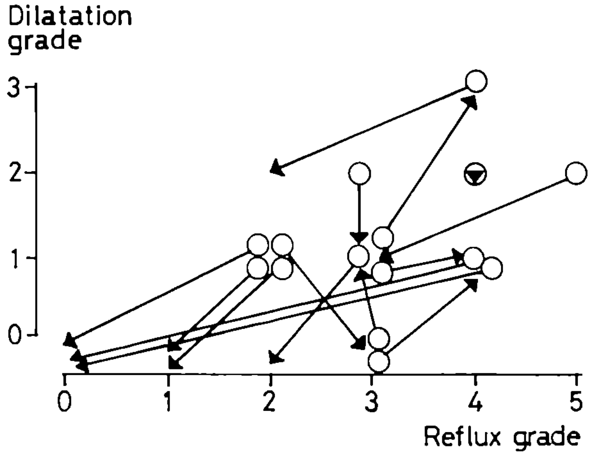

**Fig. 3** Changes in dilatation and reflux in 15 patients (13 with combined dilatation and reflux at the start of CIC and 2 with reflux at the start who acquired dilatation). Symbols as in Figure 1.

Anti-reflux operations were performed in 7 patients, 5 girls and 2 boys, a median of 2.0 years (range 1.2–3.5) after the start of CIC. The indication for surgery was a combination of dilatation of the upper urinary tract and reflux at follow-up investigation. All of these children already had reflux grades 3 to 5 at the start of CIC and 5 of the 7 also had dilatation on urography.

During CIC treatment, 3 patients were operated on and given an artificial sphincter because of severe persisting incontinence. One patient showed no improvement in urinary leakage and after 1 year the artificial sphincter was removed and CIC was discontinued; the upper urinary tract was consistently normal. After 1 to 2 years a slight transient dilatation was seen in 1 patient and this increased from slight to moderate in another.

In addition to the findings described above, 6 patients showed transient abnormalities during CIC treatment: dilatation (3), reflux (2) and both dilatation and reflux (1). Treatment by bracing was used in 22 children with severe scoliosis. Of the latter, 18 were evaluated uroradiologically; 3 developed dilatation and 2 reflux. They became normal or improved after discontinuing the brace.

Renal scarring was evident in 4 children at the start of CIC; all had reflux and 2 had dilatation as well. An additional 3 patients developed scarring during the treatment period. They had all started

CIC during the first year of life. Two of them showed reflux on all VCUs and the third had reflux on all VCUs (n = 4) after the age of 2 years.

Three adolescent patients refused to continue with CIC after 1.9 to 3 years. In all 3 the urinary tract deteriorated according to the X-rays. One girl progressed from reflux grade 3 to 4 and acquired moderate dilatation at urography; at recommencement of CIC the reflux improved to grade 1 and only slight dilatation remained. Dilatation increased from slight to moderate in 1 boy but became normal on recommencing CIC. Another boy acquired reflux grade 3 and renal scarring in addition.

## Discussion

The overall effect of CIC on the upper urinary tract was excellent. In the larger group of children with neither dilatation nor reflex at the start of CIC, the X-ray findings remained normal with a few exceptions. In children with such abnormalities, the introduction of CIC resulted most often in improvement. This was especially evident in children with isolated dilatation or isolated reflux, where complete normalization occurred in 5 of 11 and in 12 of 16 respectively. However, in patients with combined dilatation and reflux the results were more varied and in half of the children the situation remained the same or even deteriorated. Seven of the 89 patients underwent anti-reflux surgery during follow-up because of a combination of upper tract dilatation on urography and reflux of moderate to severe degree. All of these children already had reflux grades 3 to 5 at the start of CIC. Pre-existing reflux is therefore a risk factor but it should be noted that no child developed permanent reflux during CIC.

Other therapeutic measures can lead to increased difficulties in the emptying of the urinary tract. The insertion of an artificial sphincter resulted in increased dilatation in 2 of 3 patients. Treatment by bracing can have a similar effect. Three of 18 children developed dilatation when given braces but improved when this was stopped.

The importance of regular catheterisation has already been indicated by Lapides and Diokno (1972). Repeated retraining, with the emphasis on regularity, is part of our control system. We check that the technique allows complete emptying of the bladder, preferably by using an upright body position. To improve compliance, it is necessary that the patients and the family have a full understanding of the importance of these factors (Hannigan and Elder, 1988).

With the prospect of life-long CIC treatment, occasional periods with reduced attention to regularity and technique might well occur. A high risk period is during puberty, when the priorities of adolescents often change. During this period, 3 of our patients refused to carry on with catheterisation and subsequent deterioration of the upper urinary tract was seen in all of them. There may have been other children in whom CIC treatment was less than optimal and whom we did not identify because of normal radiological urinary tract findings.

This investigation covers a long period of time and the use of the same imaging techniques throughout was a prerequisite. Urography and VCU are radiographic procedures that have been carried out in basically the same way for many years at most medical centres. Radiographic films can always be re-examined because documentation is performed in a standardised fashion. In some patients it was difficult to distinguish dilatation from renal scarring and evaluation of the sequence of urographies was necessary.

Other diagnostic procedures have recently emerged that can be used to visualise the upper urinary tract. Sonography will detect dilatation, although slight and perhaps even moderate dilatation of the ureters could easily be missed (Hederström and Forsberg, 1985). A moderate degree of renal scarring is difficult to detect by sonography (Leonidas *et al.*, 1985). Today, scintigraphy is probably the method of choice to visualise renal scarring, although it may not be possible to decide whether an area with poor uptake is a permanent scar or an ongoing temporary inflammation (Shapiro *et al.*, 1988; Smellie *et al.*, 1988; Smellie, 1989).

While CIC can be depended upon to conserve normal upper tracts or to improve isolated urinary tract dilatation or reflux, we have shown that children with combined dilatation and reflux are at risk of deterioration even during CIC and they should be followed up frequently with uroradiology and other diagnostic procedures. Every effort should be made to ensure a regular and effective technique in performing CIC.

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*British Journal of Urology* (1991), 67, 420–423

# Pedicle Patch Urethroplasty

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Summary—The pedicle patch urethroplasty provides an alternative single-stage vascularised graft procedure for the repair of moderately severe hypospadias. Over a 7-year period, 38 primary hypospadias repairs were performed employing this technique. The fistula rate was 18% in the 34 patients reviewed, but there were few other significant complications. The operation is recommended when the urethral plate can be preserved and the penis straightened in boys who are unsuitable for a meatal-based flap.

A single-stage repair is desirable for all degrees of severity of hypospadias, provided the complication rate and cosmetic results are satisfactory. Many distal hypospadias repairs can be performed with a glanuloplasty (Duckett, 1981), a meatal-based flap procedure (Mathieu, 1932) or a modification of the Duplay tube principle (Duplay, 1880). These techniques will not suffice where there is a deficiency of ventral penile skin secondary to chordee, or if there is thin skin associated with hypoplasia of the corpus spongiosum and distal urethra. However, free grafts of bladder mucosa or prepuce are not advocated when the prepuce can be fashioned on a vascularised pedicle.

The pedicle patch urethroplasty can be used to compensate for the developmental deficiency of the ventral urethra in moderately severe degrees of hypospadias, provided the urethral plate is able to be preserved. The procedure has been shown to produce good cosmetic results with a low complication rate (Elder *et al.*, 1987; Hollowell *et al.*, 1990), with better results than the Duckett tube pedicle graft (Barraza *et al.*, 1987), and similar to those for the Mathieu procedure (Elder *et al.*, 1987). In the present series the pedicle patch urethroplasty was used where, after degloving the penis, the urethral plate could be preserved with the penis already straight or straightened by a Nesbit (1965) procedure.

## Patients and Methods

Between 1983 and 1989, 38 boys underwent a primary hypospadias repair using the pedicle patch procedure. The operations were carried out at 3 separate hospitals, 35 by consultant staff and the remainder by 3 registrars; 34 boys have been seen subsequently for an average 10.6 ± 8.8 months after operation. The age distribution is shown in Figure 1. The severity of deformity for each of the boys is indicated in Figure 2. If the meatus was distal in its original position, and the degree of chordee was minimal, the pedicle patch technique was chosen because of associated urethral hypoplasia.

Two patients had pre-operative testosterone to augment the penile size. Prophylactic antibiotics were given to only 8 patients; 28 were repaired with 6/0 polydiaxanone sutures for the urethroplasty and 6/0 chromic catgut (CCG) for the skin closure; 7 were sutured with polyglycolic acid. An 8 F silicone urethral catheter was used for urine drainage in 33; 2 had a urethral stent only and 3 initially had a suprapubic catheter. A silicone foam dressing was used for an average of 7 days in 35 patients and gauze was used for the remainder.

### *Pedicle patch technique*

Our operative technique is similar to that described by Elder *et al.* (1987). With the patient under general anaesthesia the meatal position, degree of chordee, urethral hypoplasia and the suitability of

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Read at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

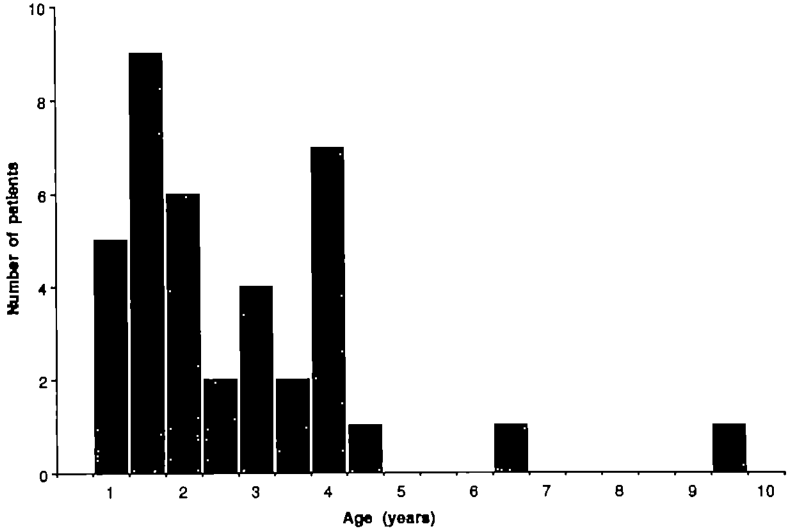

**Fig. 1** Age distribution.

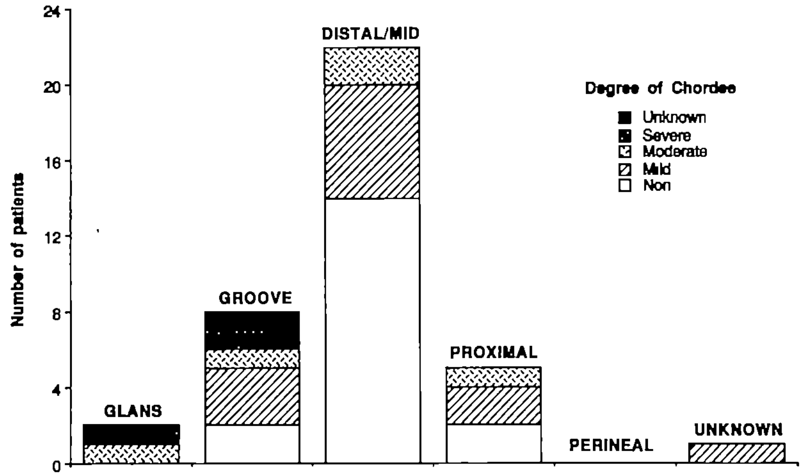

**Fig. 2** Meatal position and degree of chordee

the foreskin as a vascularised graft are assessed. The penis is then degloved, leaving the urethral plate distal to the meatus intact. A Gittes test (Gittes and McLaughlin, 1974) is performed and if glanular tilt persists, the fibrous tissue just lateral to the urethral plate is excised. The Nesbit (1965) procedure of dorsal corporal plication is performed at this stage if needed. When these manoeuvres straighten the penis, the dorsal portion of the distal neo-urethra is created by 2 parallel incisions extending on to the glans. These run distally from either side of the preserved penile shaft urethral plate to the desired position for the new meatus. At this stage lateral glans flaps are developed. If the urethra proximal to the native meatus is virtually normal, the ventral surface is incised for a short distance to allow a wide proximal anastomosis with the patch, but when the urethra is hypoplastic it is incised back to normal spongiosum tissue, as far as the penoscrotal area if necessary.

The inner layer of the prepuce is prepared and then mobilised on a vascularised pedicle down to the base of the penis, in order to prevent torsion of the shaft when the graft is rotated into position. Initially the size of the patch is not critical as it can be trimmed after the urethroplasty has commenced. After passing an 8 F urethral catheter into the bladder the anastomosis is commenced at the proximal end and continued on one side to the tip of the glans. The flap is trimmed to the correct width and length and the other side of the neo-urethra is sutured. The glans flaps are closed over the distal urethra and the proximal neo-urethra is reinforced using connective tissue of the pedicle sutured across the anastomosis.

The outer layer of the foreskin is divided dorsally and the skin rotated and closed with CCG sutures, and the dressing is applied.

## Results

The cosmetic results were generally satisfactory. No residual chordee, diverticula or proximal strictures have been seen. The complications are shown in Table 1. These are divided into minor and major, depending on whether an operation has been or will be required following the initial urethroplasty. In addition to the operative technique complications, 2 patients had a catheter blockage which required the insertion of a suprapubic catheter (1 developed a fistula). Table 2 details the outcome of the 6 fistulae and Table 3 shows the number of follow-up operations performed on six patients.

**Table 1** Complications

| *Complication* | *No. of patients* |
|---|---|
| Nil | 17 |
| Major* | |
| Fistula only | 1 |
| Fistula plus blocked catheter | 1 |
| Fistula plus infection | 2 |
| Fistula plus glans deformity | 1 |
| Meatal stenosis | 1 |
| Blocked catheter only | 1 |
| Minor† | |
| Transient fistula | 1 |
| Narrow meatus | 1 |
| Meatal retraction | 2 |
| Meatal retraction plus minimal penile torsion | 1 |
| Minimal penile torsion only | 1 |
| Glans deformity only | 3 |
| Shaft skin deformity | 1 |
| Total | 34 |

* Complications that have required or will require surgery

† Complications that were either transient or clinically insignificant.

**Table 2** Outcome of Fistulae

| *Outcome* | *No.* |
|---|---|
| Resolved | |
| Spontaneously | 1 |
| Repaired once | 3 |
| Repaired twice | 1 |
| Awaiting repair | 1 |
| Total | 6 |

**Table 3** Number of Follow-up Procedures on Six Patients

| | *No.* |
|---|---|
| Second operations | |
| Dilatation | 1 |
| Closure of fistula | 3* |
| Insertion of suprapubic catheter | 2† |
| Third operations | |
| Closure of fistula | 2*† |

* A boy who had two separate fistula operations.

† A boy who had suprapubic insertion and fistula closure.

One other boy is awaiting a fistula closure

## Discussion

One-stage hypospadias repairs became popular in the early 1970s because of the growing demand to simplify the management of the hypospadias patient. Various forms of vascularised pedicle grafts have subsequently been suggested. In general these have a lower complication rate than bladder mucosal free grafts (Duffy *et al.*, 1988) and a theoretical advantage over a prepuce free graft used by Hendren and Horton (1988).

The Hodgson III operation (Hodgson, 1970) uses the outer layer of the prepuce and dorsal penile shaft skin to form a tube pedicle. The degloved penis is passed through a buttonhole incision at the base of the penile skin which enables the neo-urethra to reach the ventral surface of the penis. Similar pedicle tubes are the basis of the Duckett tube island flap (Duckett, 1980) and the double-faced Asopa techniques (Asopa *et al.*, 1971). In the latter two, the urethra is made from skin taken from the inner layer of the prepuce.

The tube pedicle is applicable to virtually all primary repairs where chordee or urethral hypoplasia make it impossible to create a meatal-based flap, and if the foreskin is insufficient the urethroplasty can be augmented by a proximal Duplay tube (Glassberg, 1987). Furthermore, the versatility of the vascularised pedicle principle is indicated by the expanding list of indications for its use, *viz.* stricture repair (Scherz *et al.*, 1988) and penile shaft cover in hypospadias (Kaplan, 1988), epispadias (Ransley *et al.*, 1988) and buried penis surgery (Wollin *et al.*, 1990).

Operations devised to preserve the distal urethral plate and incorporate a vascularised flap into the construction of a neo-urethra include the Hodgson II procedure (Hodgson, 1970), which uses the outer layer of the prepuce after the penis has been passed through a buttonhole in the foreskin, and the pedicle patch as described by Elder *et al.* (1987), which enables the inner layer of the foreskin to be used for the ventral surface of the constructed urethra, leaving the outer layer of the prepuce available to cover the shaft of the penis.

The pedicle patch is generally used for less severe hypospadias than is the Duckett tube repair, and better results should therefore be expected for those boys who have a pedicle patch procedure. Our fistula rate for the Duckett procedure when used for primary hypospadias repairs, over the same period, was 34.4% (Dewan *et al.*, unpublished data). Conversely, Elder *et al.* (1987) reported a lower complication rate for the pedicle patch than for the Mathieu procedure, as did Hollowell *et al.* (1990). Both of these reports attributed the improvement on the Mathieu results to the elimination of the hypoplastic distal urethra which remains in some patients who have a meatal-based flap repair. Hollowell *et al.* (1990) found an overall complication rate of 8% for 31 boys who were seen no less than 12 months after surgery, compared with a 10% complication rate for the 34 who had a Mathieu operation. Our fistula rate (18%) is probably higher than in this study, but their complications are not listed in detail and only 31 of the 66 pedicle patch cases seen during the study period are included.

Despite our 6 fistulae, the necessity for reoperation was minimal and the fistulae were easily managed. The cosmetic results were satisfactory, without residual chordee, stricture or diverticulum.

The pedicle patch procedure allows for single-stage management of moderately severe hypospadias when the urethral plate can be preserved, while avoiding the complications of the tube pedicle graft. It is a useful addition to the MAGPI, Mathieu and Duckett procedures for primary hypospadias, particularly as the vascularised flap principle is useful for other types of penile surgery.

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# One-stage Hypospadias Repair: Experience of 367 Cases

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Summary—Over a 6½-year period we performed 374 primary hypospadias repairs, all but 7 as single-stage procedures. We usually employed the MAGPI, tubed preputial island flap and Mathieu reconstructions. Complications were comparatively few, with an overall incidence of 5% fistulae, 3% anastomotic strictures and 7% meatal retraction or stenosis. The cosmetic results were superior to those of staged procedures in that it was almost always possible to obtain a glanular meatus which was both terminal and realistic.

In recent years the surgical management of hypospadias has been characterised by 2 inter-related trends—firstly towards single rather than staged repairs and secondly toward procedures intended to give cosmetically as well as functionally satisfactory results. Nonetheless we are aware that traditional staged procedures, notably the Denis Browne (Browne, 1949) and variants (Crawford, 1963), remain popular with surgeons in the United Kingdom and have the virtues of proven durability and a recognised rate and variety of complications. Do their single-stage successors give demonstrably superior results? We review our experience.

## Patients and Methods

All single-stage primary hypospadias repairs performed in this unit from 1 October 1983 to 28 February 1990 have been reviewed. We employed MAGPI (Duckett, 1981b), tubed preputial island flap (TPIF) (Yaxley, 1968; Duckett, 1981a), Mathieu (1932), onlay island flap (OIF) (Elder *et al.*, 1987) and van der Meulen (1977) reconstructions. The indications were those described by their originators, with choice determined by the interplay of meatal site, presence or absence of chordee and extent of any distal urethral hypoplasia. As a rule we found that all but minor degrees of distal urethral hypoplasia were associated with chordee correctable only by urethral mobilisation and hence TPIF reconstruction, but on occasions where there was no chordee, OIF repair was employed in preference to Mathieu or MAGPI procedures. The van der Meulen repair, performed only early in this series, was used in situations otherwise suitable for MAGPI, Mathieu or OIF reconstructions. The procedures were performed largely as described by their originators. Meatotomy in the MAGPI procedure was found to be better effected by knife than by scissors. The TPIF procedure was modified by incorporating a 'V' flap on the glans (Fig.) in the hope of preventing meatal stenosis; in constructing the proximal anastomosis, all hypoplastic urethra was excised and spatulation was such that the circumference was approximately twice that of the urethra originally. Where there was deficiency of skin ventrally, Byars flaps were employed, disposed vertically rather than transversely for preference.

At first we experimented with details of surgical technique and with varieties of catheter drainage and dressing but during the last 5 years our practices were standardised. Caudal anaesthetic block and artificial erection (Gittes and McLaughlin, 1974) were routine. We employed neither optical magnification nor diathermy. Haemostasis was achieved by infiltration of 1 to 2 ml of 1 in 100,000 adrenalin

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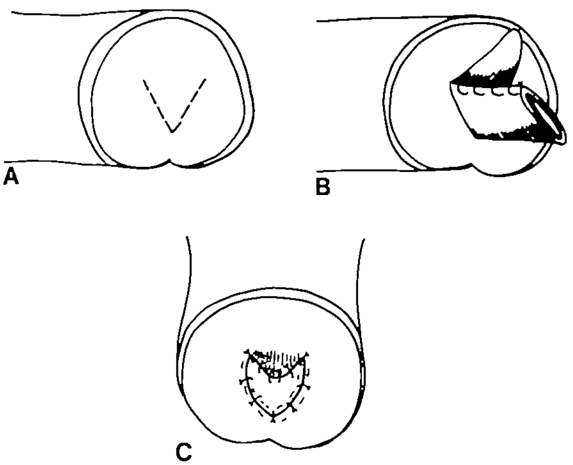

**Fig.** Modified meatal construction for tubed preputial island flap repair. (A) A 'V' flap is cut at the apex of the glans. (B) The flap is raised and the neo-urethra drawn through the glans tunnel. (C) The 'V' flap is inset to the spatulated distal neo-urethra.

solution, supplemented, as necessary, by penile tourniquet, usually when raising glans flaps for Mathieu or OIF procedures. Chromic catgut (5–0) was used for skin suture, braided polyglactin (Vicryl) otherwise, 6–0 for urethral construction and anastomosis, 5–0 for MAGPI procedures and 4–0 for glans wrap with Mathieu and OIF repairs. Catheters were not used with MAGPI repairs. With other procedures, bladder drainage was via a per-urethral soft silicone rubber tube, 9 F, with side-holes cut in its proximal extremity and secured to the glans with the silk suture used for traction per-operatively. Catheters were removed 7 days after the Mathieu repair and 10 days following other procedures. Antibiotic prophylaxis was administered during the period of catheter drainage and oxybutynin was given in the event of detrusor spasm; 2-cm ribbon gauze soaked in compound tincture of benzoin was used for dressing MAGPI repairs. For other procedures, silicone foam (De Sy and Osterlinck, 1982) was used and left undisturbed until the time of catheter removal.

It was general policy to undertake MAGPI repairs at 12 to 18 months of age and other procedures at 30 to 36 months.

## Results

### *General*

During the period reviewed, we performed 374 primary hypospadias repairs; 7 patients with severe perineal hypospadias had staged procedures. The principal complications of the 367 single-stage procedures are set out in the Table.

### *MAGPI Repairs (n = 216)*

Age at surgery ranged from 4 to 183 months (mean 38). The meatal site was glanular in 42 cases, coronal in 164 and subcoronal in 10. Twenty-four boys had mild or moderate chordee; in 18 instances this was corrected by mobilisation of skin from the penile shaft and excision of adventitial tissue overlying the ventral aspects of corpora and urethra; in the remaining 6 cases final correction was achieved by insertion of tucking sutures (3–0 white silk) dorsally in Buck's fascia. Any perceived deficiency in skin cover ventrally was corrected by Byars flaps.

Immediate post-operative complications were few and included 3 examples of secondary haemorrhage and 2 of urinary retention. Seven patients had catheter drainage for up to 5 days post-operatively and 11 stayed in hospital beyond 1 day post-operatively.

In 197 cases (91%) the result was cosmetically and functionally satisfactory after the initial procedure. The principal complication, partial or complete meatal contraction, occurred on 16 occasions. In 7 instances the original meatal site had been subcoronal. Six patients had no functional impairment, with a normally directed urinary stream, and had no further surgery. Ten patients

**Table** Principal Complications of 367 One-stage Repairs

| *Procedure* | *No.* | *Fistula No. (%)* | *Stricture No (%)* | *Meatal retraction/ stenosis No. (%)* | *Other No. (%)* |
|---|---|---|---|---|---|
| MAGPI | 216 | 3 (1) | — | 16 (7) | 1 (0.5) |
| TPIF | 100 | 9 (9) | 12 (12) | 4 (4) | 3 (3) |
| Mathieu | 34 | 2 (6) | — | 3 (9) | — |
| Others | 17 | 4 (24) | — | 3 (18) | 7 (22) |
| Total | 367 | 18 (5) | 12 (3) | 26 (7) | 11 (3) |

had a repeat MAGPI procedure, with 7 having a good functional and cosmetic result. Follow-up did not usually extend beyond one return visit 1 to 3 months post-operatively, but 29 patients were seen a year or more after the repair and among these there were no examples of late meatal retraction as described by Hastie *et al.* (1989).

On 3 occasions the urethra was entered subcoronally during ventral mobilisation of skin and in 2 instances this was followed by fistulation. The remaining fistula occurred some distance subcoronally and the cause was unclear. All fistulae were corrected by a single further procedure, as were fistulae following other types of repair.

### *Tubed Preputial Island Flap Repairs (n = 100)*

Age at surgery ranged from 14 to 176 months (mean 38). The meatus lay subcoronally in 47 patients, mid-shaft in 46 and penoscrotal in 7. Chordee was present in all but 5 cases and was severe in 23. On 22 occasions a degree of chordee persisted despite adequate urethral mobilisation and excision of all fibrous tissue overlying the ventral and lateral aspects of the corpora; final correction was achieved by dorsal tucking sutures. Flap length ranged from 1.7 to 4.8 cm (mean 3.1). As a rule, ventral skin cover was by Byars flaps disposed vertically; a 2-faced flap (Duckett, 1986) was employed on one occasion.

Immediate post-operative complications (apart from detrusor spasm) were confined to 4 patients who required catheter replacement after premature dislodgement. In 72 instances the initial result was entirely satisfactory. The commonest complication, stricture of the proximal anastomosis, occurred on 11 occasions and was always symptomatically evident within 2 months of surgery. This complication was not related to flap length but did appear to be related to experience, with 9 occurring in the first 50 cases and 3 in the second 50, possibly because greater care was taken to excise hypoplastic urethra and to spatulate the anastomosis as widely as possible. Eight strictures were cured by a combination of urethrotomy and dilatation whilst 4 required open revision. The incidence of fistulae was not related to experience but was associated with flap length, with an incidence of 6/29 (21%) where flap length exceeded 3.5 cm and 3/71 (4%) with shorter flaps. In 2 of the latter cases, there was tension at the suture line because the flap had been cut rather short. In 8 cases early in the series glans wrap was employed (Parsons and Abercrombie, 1982) rather than glans tunnel and both examples of meatal retraction occurred in this group. Two patients developed meatal stenosis, neither having had a 'V' flap cut on the glans. The 3 other complications were skin redundancy requiring trimming and the same procedure was performed in 4 further cases coincident with stricture or fistula repair.

### *Mathieu Repairs (n = 34)*

Age at surgery ranged from 18 to 156 months (mean 45) and the meatal site varied from 2 to 5 mm subcoronally. Flap lengths ranged from 1 to 1.7 cm. There were no immediate complications and late complications included 3 cases of meatal retraction, corrected by MAGPI advancement, and 2 cases of fistula; 85% of patients had a satisfactory result following the initial procedure.

### *Onlay Island Flap Repairs (n = 9)*

As mentioned previously, this procedure was restricted to those few patients who had a subcoronal meatus combined with distal urethral hypoplasia but without chordee. Late complications included fistula (3), meatal retraction (2) and skin redundancy (2), so that only 2 patients had a satisfactory initial result.

### *van der Meulen Repairs (n = 8)*

Two patients had a major complication (1 meatal retraction, 1 fistula) and 5 had skin redundancy and/or residual torsion requiring a secondary procedure. Thus only 1 patient had a satisfactory result following the initial procedure.

## Discussion

The quest for perfection in the surgical treatment of hypospadias must continue. Of the factors impeding that goal, technical minutiae might seem the least consequential. From time to time it is suggested that various types or gauge of suture material, means of catheter drainage, modes of dressing, etc, are in some degree critical to success or failure. This we doubt, making no such claim for the methods we employ, and suggest that the end result is dependent upon more mundane factors, namely a limited repertoire of inherently sound procedures, choice appropriate to the case in hand and the experience of the operator.

Our current repertoire is not all-embracing, but its limited range enables single-stage repair of all but a few cases with severe perineal hypospadias and, at the same time, allows the operator to become thoroughly familiar with each technique. Some years ago we reported good results with the van der

Meulen reconstruction (Gipson and Rickwood, 1979) and abandoned it only because, in our hands, good cosmetic results were more consistently achieved by other means. Some authorities have effected single-stage reconstruction of perineal hypospadias by extending TPIF repair (Duckett, 1986; Glassberg, 1987) but in our patients with this deformity the prepuce itself was under-developed and too narrow to create a neo-urethra of sufficient length. Use of a free graft of bladder mucosa would represent an alternative strategy in this situation (Mollard *et al.*, 1987). Although the indications for the procedures which we employ are usually clear-cut, there is some room for divergence. In Manchester, for example, the proportion of MAGPI and Mathieu repairs is the reverse of that described here (Gough, personal communication).

The MAGPI procedure undoubtedly represents a major advance in the management of minor hypospadias, having few complications and giving consistently good results (Ozen and Whitaker, 1987) which, at their best, are virtually indistinguishable from a normal circumcised penis. In the past, an appreciable number of present recipients, principally those with a glanular meatus, would have had no repair at all or, perhaps, a meatotomy only. Satisfactory results are obtainable in the presence of a minor degree of chordee (Ozen and Whitaker, 1987) but not consistently if the meatus is truly subcoronal, especially if there is any degree of distal urethral hypoplasia. The functional result, *i.e.* the direction of the urinary stream, appears to depend more upon the execution of the meatotomy than the glans wrap and may thus be satisfactory even with meatal retraction. Nonetheless, the ideal is a terminal meatus. Anything less should be judged a failure and a repeat procedure is often worthwhile. Where doubt exists at the outset, a Mathieu repair is usually advisable. This procedure, now enjoying a belated renaissance, gives consistently good results but is comparatively rarely indicated. More so still, in our experience, is the onlay island flap; the indifferent results we obtained were almost certainly a reflection of inexperience rather than any inherent limitations of this reconstruction.

For more severe hypospadias, the TPIF procedure also represents a useful advance, with other centres reporting results comparable to our own (Duckett, 1981a; Man *et al.*, 1986; Barraza *et al.*, 1987). The repair is comparatively complex and not one for the occasional operator. Although it is based upon the notion that a vascularised flap is essential for success, similar results have been reported employing a free graft of preputial lining (Devine and Horton, 1977) and the choice between these procedures is one of personal preference. The principal complications, fistula and stricture, relate to the proximal anastomosis and could be due to flap ischaemia. Our results suggest that this might be true of fistulae but not of strictures. The latter, we feel, derive from the urethra proper rather than from the graft and can best be minimised by a widely spatulated anastomosis to good quality urethra. Meatal stenosis is a rare complication and did not occur in the present series when a glans flap had been incorporated. Flaps used for ventral skin cover often appear of tenuous vascularity and minor degrees of necrosis were common. This appears to be inconsequential and we found that final appearances were generally superior where there had been a little tension on the ventral suture lines.

The traditional staged repairs could be said to have stood the test of time mainly because nothing better existed. When compared with 1-stage repairs they have a 100% complication rate from the outset and in some hands (Smith *et al.*, 1976; Rees *et al.*, 1981), if not all (Crawford, 1963), there is a high incidence of further unplanned procedures beyond that principally relating to urethral fistulae. Single-stage repairs obviously entail less surgery and their complication rate is probably lower than that of their staged predecessors. Continued use of the latter could be justified only should there prove to be late complications of 1-stage repairs yet to become apparent, or if they produce a demonstrably superior cosmetic result. The former seems unlikely; some of the procedures employed here were introduced over 10 years ago (and much longer with the Mathieu procedure) and many early recipients must now have reached sexual maturity without reported problems. The functional results of staged procedures are generally satisfactory but cosmetically leave something to be desired; in particular, it is rarely possible to obtain a meatus which is both terminal and realistic.

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# Long-term Follow-up of Children with Testicular Tumours: Surgical Issues

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Summary—Testicular tumours are rare in childhood. The clinical, pathological and follow-up details of 48 children are presented. The combined approach of surgery, chemotherapy and radiotherapy is confirmed as being extremely effective. Transcrotal orchiectomy is not an appropriate surgical procedure. Testicular biopsy is detrimental to prognosis.

Tumour of the testis is a rare but potentially lethal condition in the paediatric population, accounting for less than 1 to 2% of all solid tumours. The comparative rarity of this condition has resulted in the development of multicentre trials of management in each of the different pathologies which can arise (Mann *et al.*, 1989.) The aim of this study was to assess our own experience and examine the outcome following surgery.

## Patients and Methods

A review of the records at the Manchester Childrens' Tumour Registry disclosed relevant data on 48 patients with testicular tumours in the period from 1954 to 1989. The case records were surveyed and information was abstracted concerning the clinical findings, surgery, histopathology, adjuvant therapy and outcome. In addition to clinical and surgical assessment, histological diagnosis was confirmed by a board of eminent tumour histopathologists.

## Results

This study confirmed the wide range of pathologies which may affect the testis; with yolk sac tumour affecting 19 boys, teratoma (19), rhabdomyosarcoma (6) and rare tumours (4) (Table 1). Eight children died from their testicular tumour and their details are listed in Table 2.

**Table 1** Histopathology of Primary Testicular Tumour (and Related Mortality)

| *Histology* | *No* | *Deaths (%)* |
|---|---|---|
| Yolk sac tumour | 19 | 4 (21) |
| Teratoma | 19 | 1 (5) |
| Rhabdomyosarcoma | 6 | 3 (50) |
| Primary lymphoproliferative disease | 3 | – |
| Leydig cell tumour | 1 | – |
| Total | 48 | 8 (16.6) |

The overall annual incidence of testicular tumours did not vary during the period of review except for a short period in the early 1970s (Fig.). Of the children who succumbed to the disease, only 2 presented in the earlier pre-chemotherapy period of the study.

### Yolk sac tumours

Nineteen patients had yolk sac tumours. The mean age at presentation was 1.9 years (range 9 months–5 years) and more than 85% were less than 2 years old. All presented with painless scrotal swelling.

For staging purposes the British system was used (Peckham and McElwain, 1976). Stage 1: tumour confined to the testis; stage 2: tumour confined to the testis and retroperitoneal/abdominal lymph nodes; stage 3: tumour spread to supradiaphrag-

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**Table 2** Mortality statistics

| *Tumour type* | *Age (years)* | *Year* | *Treatment delay (months)* | *X-ray therapy* | *Chemotherapy* | *Survival (months)* |
|---|---|---|---|---|---|---|
| YST | 0.75 | 1970 | 1 | + | + | 11 |
| YST | 1.5 | 1960 | 0.5 | – | – | 9 |
| YST | 1 | 1971 | 2 | + | + | 7 |
| YST | 1 | 1971 | 12 | + | + | 36 |
| YST | 2 | 1978 | 6 | + | + | 18 |
| ERMSA | 2 | 1970 | 0 5 | + | + | 12 |
| ERMSA | 3.5 | 1954 | 3 | + | – | 35 |
| ERMSA | 9 | 1980 | 6 | + | + | 36 |

YST = Yolk sac tumour
ERMSA = Embryonal rhabdomyoscarcoma.

matic lymphatics; stage 4: extralymphatic spread. Accordingly, 15 patients had stage 1 disease, 1 had stage 2 and the remaining 3 patients had stage 4 disease.

In 14 patients orchiectomy was performed via an inguinal approach; 3 had a transcrotal procedure and 2 underwent testicular biopsy, with subsequent inguinal orchiectomy once the diagnosis was confirmed. Groin exploration and cord resection were carried out later in 4 cases, 1 patient had an exploratory laparotomy for intra-abdominal disease and 1 underwent a further scrotal exploration. Ten patients received multimodal chemotherapy and 3 underwent radiotherapy.

Four patients died, 3 within 12 months of diagnosis and the other at 3 years, giving an overall mortality rate of 21%. Two of these patients had scrotal exploration and 1 subsequently developed scrotal and groin recurrence. One patient died in the earlier period of the study and received no adjuvant treatment. The other 3 received chemotherapy and radiotherapy before their demise. Chemotherapy consisted mainly of vincristine, cyclophosphamide and Adriamycin (VAC) in cyclical combination, but combinations including etoposide, platinum compounds and vinblastine were administered for the more advanced and resistant tumours. The interval between clinical presentation and surgical treatment in those who died was 2 weeks, 1 month, 2 months and 6 months.

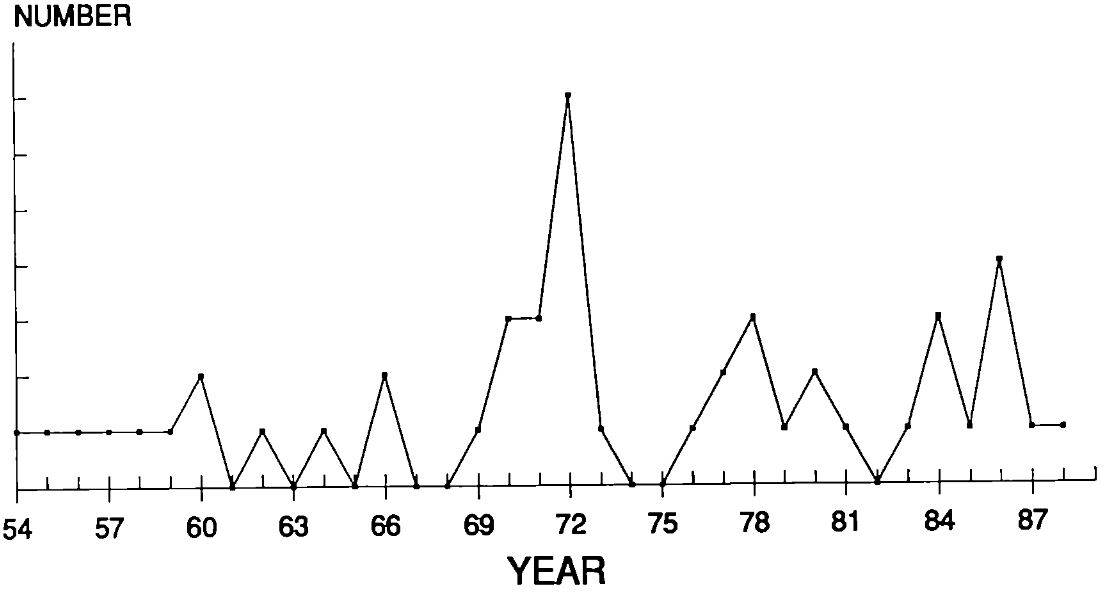

Fig. Annual incidence of testicular tumours.

### *Teratoma*

Teratoma was diagnosed in 19 patients; 15 had benign disease but 4 had malignancy. While diagnosis at that time was suggestive of malignant teratoma, subsequent histopathological review revealed the pathology to be teratoma with malignant yolk sac elements. The mean age at presentation was 3 years (range 7 months–12 years). Fourteen children complained of painless testicular swelling, 3 had testicular pain and 2 had abdominal discomfort. One child presented with acute testicular pain necessitating emergency exploration and orchiopexy. It was only when swelling persisted that an underlying pathology was suspected and histology confirmed teratoma with malignancy. Two of the patients with malignancy had local disease and the other 2 were stage 4 with distant metastases.

Seventeen children underwent groin exploration and orchiectomy but 2 had scrotal excision of the testis as primary treatment. One patient underwent attempted aspiration of a cystic teratoma. Two of the children with malignant disease received chemotherapy and radiotherapy and the remaining 2 were cured with radical surgery. Chemotherapy consisted of vincristine, Adriamycin and cyclophosphamide (VAC) in 1 case and combinations of vinblastine, cisplatin, prednisolone, etoposide and radiotherapy in the other. One patient died from widespread metastatic disease 18 months after diagnosis and 1 boy is currently receiving intensive therapy for pulmonary metastatic disease.

### *Rhabdomyosarcoma*

Six patients were diagnosed as having rhabdomyosarcoma of the paratesticular tissues. Their mean age at presentation was 5 years (range 0.5–13). Five boys presented with asymptomatic swelling and 1 with a painful tender testis. High inguinal orchiectomy was performed in 4 cases. One patient underwent scrotal exploration, frozen section biopsy and orchiectomy which was followed by inguinal resection of the spermatic cord at a later date. In the remaining patient, attempted aspiration of the scrotal swelling preceded orchiectomy, which was performed several months later when the swelling persisted. Two of the boys underwent later staging laparotomy and inguinal nodes were biopsied in another. The histology was embryonal rhabdomyosarcoma in 5 boys and the sixth had undifferentiated sarcoma. Five received combination chemotherapy and radiotherapy. One patient who presented in the early period of the study received radiotherapy alone but the remainder had treatment regimes of actinomycin D, VAC and cisplatin.

There were 3 deaths in this group, occurring 3 years after diagnosis in 2 patients and after 1 year in the third, with all patients succumbing to metastatic disease despite intensive adjuvant therapy. One of the deaths followed attempted aspiration of the scrotal swelling. The interval between clinical presentation and definitive surgical treatment in the children who died was 2 weeks, 3 months and 6 months.

### *Lymphoma*

Three patients had lymphoma. Their mean age at presentation was 7 years (range 3–12). All presented with painless swelling of the testis and the diagnosis was made only after histological analysis since there were no other signs of lymphoproliferative disease. Two patients received adjuvant therapy but no other focus of lymphoma was identified in the third and treatment was not indicated after orchiectomy. Two underwent inguinal orchiectomy and the third had scrotal surgery followed by inguinal cord resection when the diagnosis was made. All continue to be well, with no sign of recurrence.

### *Leydig cell tumour*

One patient presented at the age of 7 years with penile development, pubic hair and formed testes, with the right testis noticeably larger than the left. Histology confirmed the lesion to be non-invasive Leydig cell tumour. This was successfully treated by local excision.

## Discussion

Yolk sac tumours are reported to be the commonest histological type of testicular tumour encountered in paediatric practice (Kaplan *et al.*, 1989). However, only 39% of our patients had a yolk sac tumour. A recent report by Mann *et al.* (1989) on the outcome in children with malignant germ cell tumours (including 61 boys with testicular yolk sac tumours) describes very encouraging survival statistics based on intensive adjuvant chemotherapy and prolonged monitoring of tumour markers (AFP/HCG).

Surgery is often curative in the majority of cases, since most present with stage 1 disease. However, patients with advanced disease are difficult problems and our own statistics reflect this, since 30% of those who relapse with metastases do not respond to further treatment (Kaplan *et al.*, 1989).

Teratoma is the commonest benign tumour of the testis. It has been claimed that these testicular tumours are invariably benign (Jones and Cambell, 1976). However, 4 of the 19 patients in this study were confirmed to have malignant yolk sac lesions arising in teratomatous tumours and, with this in mind, attention must be paid to the histological diagnosis, pre-operative assessment of potential metastatic deposits and long-term follow-up of the tumour markers alpha-fetoprotein and beta-HCG.

Paratesticular rhabdomyosarcoma arises in the mesenchymal elements of the spermatic cord and may directly involve the testis and scrotal tissues (Olive *et al.*, 1984). The most common histological type is embryonal rhabdomyosarcoma (Raney *et al.*, 1987) and despite the advances in adjuvant chemotherapy and radiotherapy, death occurs in 35% (LaQuaglia *et al.*, 1989). Significant predictors of fatality include unresectability and the presence of metastatic disease at the time of presentation. Early diagnosis and treatment, therefore, should improve the outcome. Retroperitoneal lymph node dissection has been shown to offer no therapeutic advantage and its only role lies in improving the accuracy of staging (Olive *et al.*, 1984). With recent advances in imaging techniques (*e.g.* computed tomography and magnetic resonance imaging) the role of lymphatic dissection in the management of rhabdomyosarcoma is questionable.

Metastatic involvement of the testis is usually secondary to leukaemia or lymphoma. It is therefore uncommon for the children to present with testicular swelling and, when encountered, orchiectomy followed by systemic chemotherapy and local radiotherapy is the recommended treatment.

The treatment of neoplastic disease of the testis is one of the success stories of current times, with remarkable improvements in prognosis even in the presence of advanced metastatic disease (Mann *et al.*, 1989). However, mortality can still occur. As with other malignant disease, earlier diagnosis leads to earlier treatment, as demonstrated by the high cure rate in stage 1 disease (Flamant *et al.*, 1986). Despite this simple truth, patients are still referred to specialist centres with delays of up to 6 months following initial presentation to their family doctor or district hospital. A child with a suspicious testicular swelling requires urgent referral to a centre with the appropriate facilities for investigation and treatment.

Controversy exists concerning the surgical approach to testicular pathologies. The scrotal approach reportedly enhances the risks of local seeding and metastatic spread (Peckham and Hendry, 1987). In the United States, hemiscrotectomy is advocated when the scrotum has been violated (Fernandes *et al.*, 1989). However, it is clear that scrotal surgery has little or no influence on the outcome when there is advanced disease and may only affect stage 1 disease (Ozen *et al.*, 1988). In addition, failure to perform inguinal lymphadenectomy does not reduce survival. Consequently, radical scrotal surgery has not gained wide acceptance in this country.

Despite the rarity of testicular tumours, the risk of local tumour contamination and dissemination is real. Our experience confirms the existence of such hazards and the literature emphasises that scrotal violation should be avoided (Ozen *et al.*, 1988). When a child presents with an atypical scrotal swelling, ultrasonography will differentiate a solid lesion from a hernia or hydrocele (Raney *et al.*, 1987).

A recurring factor throughout this study has been the late presentation of patients with testicular swelling. It is impossible to assess the effect of this on eventual outcome during the course of a retrospective study. However, there is considerable evidence that earlier diagnosis leads to high rates of cure in the adult population and little to suggest that children will behave differently (Ellis and Sikora, 1987). Attempts have been made to improve public knowledge and understanding of testicular tumours in the adult population (British Medical Journal, 1980; Lancet 1980). It is clear that the profession itself requires some re-education with regard to the management of testicular swelling and tumours in children.

Thorough examination and history-taking are essential in the assessment of a child with atypical scrotal swelling. Ultrasonography is especially useful in problematic cases (Howe *et al.*, 1988). The appropriate surgical procedure is orchiectomy performed through an inguinal approach, and incisional or needle biopsy should be avoided. If the diagnosis is either suspected clinically or confirmed histologically, prompt referral to an appropriate centre is essential to co-ordinate chemotherapy, radiotherapy and any further surgery that may be necessary.

## Acknowledgements

We thank Dr Gillian Birch and the staff at the Manchester Children's Tumour Registry, which is supported by the Cancer Research Campaign, and Dr P. E. Campbell, Director of Anatomic Pathology, Royal Children's Hospital, Melbourne, for advice concerning histological classification.

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# Case Reports

## Prostate Carcinoma Metastatic to the Male Breast

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### Case Report

A.S. was referred to this department in September 1988 with metastatic prostate carcinoma. Two years previously he had presented elsewhere with abdominal pain and weight loss. Cervical lymphadenopathy was noted and biopsy revealed poorly differentiated adenocarcinoma in the lymph nodes. Computed tomography at that time revealed retroperitoneal lymphadenopathy and the patient received chemotherapy. Three months later sclerotic bone metastases were noted, a diagnosis of prostatic carcinoma was made and the patient was treated with stilboestrol with a good response. In May 1988 he was seen by the Radiotherapy Department at this hospital with severe bone pain and was treated by half-body irradiation, again with a reasonable response. At this stage he stopped using stilboestrol. When seen by us he complained of weight loss, pain, enlarged lymph nodes and painful enlarged breasts. On examination he was cachexic and cervical and axillary lymphadenopathy was noted. There was also marked bilateral gynaecomastia which was stony hard in consistency. Rectal examination revealed a small clinically benign prostate. Total acid phosphatase was raised at 324.2 u/l (normal range 4.8–13.5) with a prostatic fraction of 272.7 u/l (normal $<3.7$). Alkaline phosphatase was 235 u/l (normal range 30–85) and lactate dehydrogenase 662 u/l (normal range 100–350). A radioisotope bone scan revealed multiple metastases. Bilateral orchiectomy was performed together with biopsy of the unusually hard gynaecomastia under local anaesthesia.

Histology revealed male breast tissue invaded by poorly differentiated adenocarcinoma cells which stained positively for both prostatic acid phosphatase and prostate specific antigen (PSA) using immunohistochemical staining with polyclonal antibodies (Fig.).

Despite the reintroduction of hormonal treatment the patient deteriorated rapidly and died 3 months later (December, 1988).

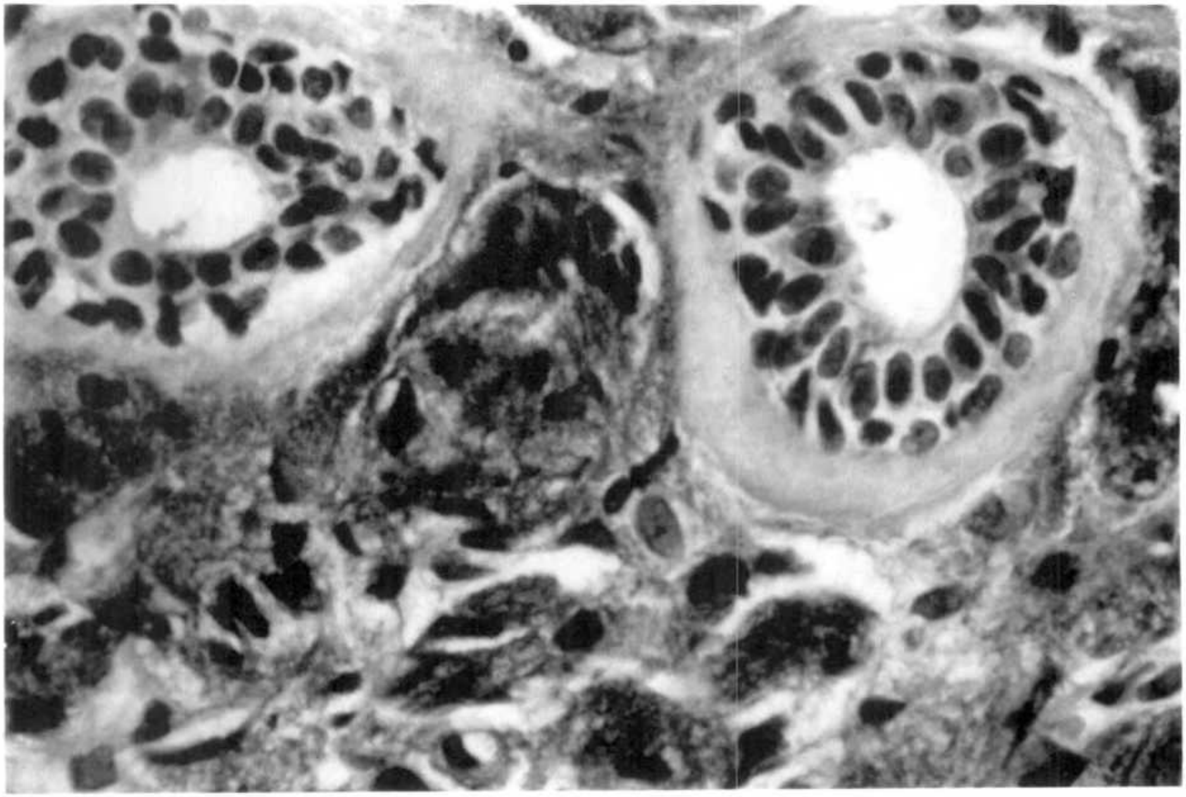

**Fig.** Two normal breast ducts and numerous carcinoma cells staining positively for PSA. (× 400).

### Comment

Prostate carcinoma is classically associated with osseous or lymphatic metastases, but unusual sites of metastases have been reported and immunohistochemical staining techniques have proved valuable in localisation of metastatic adenocarcinoma to a prostatic origin (Venable *et al.*, 1983). Metastatic prostate carcinoma to the breast is uncommon and although proof of the prostatic origin has been lacking in most early reports, Naritoku and Taylor (1983) reported 2 cases where immunocytochemical demonstration of PSA and prostatic acid phosphatase were performed. Most of the earlier cases have been associated with diffuse metastatic disease and the patients were on oestrogen treatment when the breast malignancy was discovered (Drelichman *et al.*, 1980). One can only speculate as to whether gynaecomastia associated with oestrogens, by increasing local blood supply, encourages metastases to this site.

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## An Unusual Case of Bladder Perforation

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### Case Report

A 53-year-old male presented with several episodes of lower urinary tract infection despite appropriate antibiotic therapy.

Eleven years previously he had survived an anterior wall myocardial infarction and 5 years previously an automatic defibrillator had been implanted after episodes of severe ventricular arrhythmia; 3 years previously the defibrillator had been replaced with an automatic cardioverter-defibrillator which was implanted into a previous left abdominal pocket. Since the patient showed no arrhythmia during several Holter monitor recordings, the defibrillator was deactivated.

Intravenous urography was performed because of the persistent urinary tract infection and this suggested the presence of defibrillator leads within the bladder. This was confirmed by cystoscopy.

We extracted the defibrillator and sutured the urinary bladder. The leads were left properly fixed into the rectus muscle. The patient's clinical course was uneventful.

### Comment

In a series of 112 patients receiving this implant this complication did not occur (Mirowski, 1985) and in our patient it was due to pressure necrosis with perforation of the roof of the bladder.

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## Combination of Chemolysis and Extracorporeal Shock Wave Lithotripsy in Cystine Urolithiasis

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Extracorporeal shock wave lithotripsy (ESWL) and endoscopic contact lithotripsy have failed to disintegrate cystine calculi (Dretler, 1988) but the newer extracorporeal lithotriptors cause fragmentation of cystine stones and, when combined with intensive chemolysis, accelerate dissolution by increasing the contact surface for chemolytic agents (Schmeller *et al.*, 1984).

### Case Report

A 50-year-old female presented with left colicky pain. A right nephrectomy had been performed previously because of pyonephrosis due to an infected staghorn stone and analysis confirmed it was composed of cystine. Despite preventive medical treatment, a left staghorn stone recurred within 6 years.

ESWL monotherapy (Vandeursen and Baert, 1990) was started with a Lithostar (Siemens, Erlangen, Germany) on an out-patient basis without anaesthesia. Despite progressive disintegration, a 9-mm sacro-iliac obstructive fragment developed (Fig. 1). Anuria necessitated nephrostomy. A single ESWL treatment was performed, with a total of 4000 shock waves at 18.1 kV, with fragmentation. Continuous alkalinisation and irrigation with N-Acetyl-L-Cysteine then commenced through the nephrostomy, at a rate of 1 L/h, with the following solution: 880 ml *aqua destillata* + 300 mEq $NaHCO_3$, 120 ml N-Acetyl-L-Cysteine. Complete dissolution within 3 days was confirmed by nephrostomography (Fig. 2).

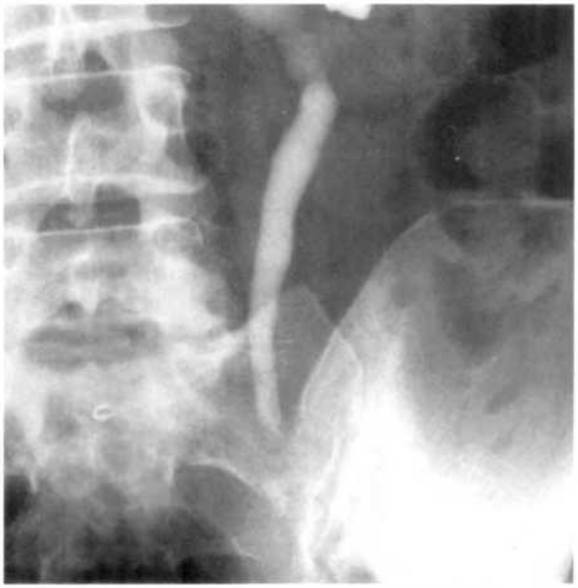

**Fig. 1** Nephrostomogram showing obstructive calculus in the sacroiliac ureter.

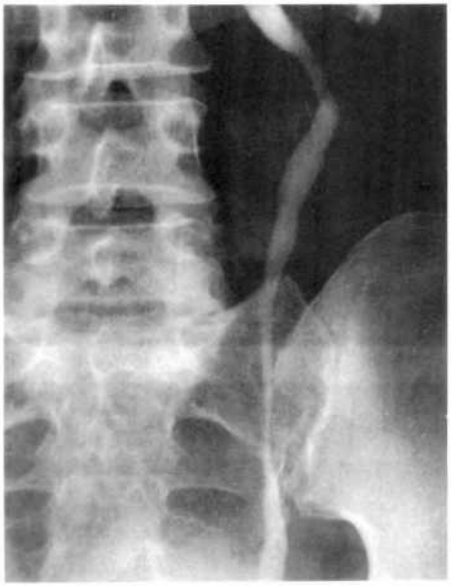

**Fig. 2** Nephrostomogram showing complete dissolution of stone within 3 days.

## Comment

Complete stone dissolution has been achieved by chemolysis, the most effective agent being N-acetylcysteine in an alkaline solution.

Intervals to complete stone dissolution have ranged from 9 to 42 days (Smith *et al.*, 1979; Dretler *et al.*, 1984). Acetylcysteine is thought to act by opening disulfide bonds and thus reducing the dimer cystine to the more soluble monomer cysteine (Mulvaney *et al.*, 1975). The time required for complete dissolution of cystine stones can be reduced by using a combination of chemolysis and ESWL.

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# Prolapsing Urethral Polyp in an Epispadiac Urethral Duplication

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Congenital urethral polyp and urethral duplication are both rare anomalies. We report what we believe to be the first case of a fibroepithelial polyp occurring in an infant with an incomplete epispadiac duplication.

## Case Report

A newborn healthy male was noted to have a polypoid mass prolapsing from a wide mouth midshaft epispadiac urethral meatus. In addition a normal urethral meatus opened at the tip of the glans. There was an epispadiac glanular groove and marked dorsal chordee (Fig. 1). serum electrolytes, renal and bladder sonography and voiding cystourethrography were normal. Retrograde urethrography through the epispadiac meatus showed the accessory urethra to be a thin tube coursing dorsal to the normal urethra and ending blindly deep to the symphysis pubis (Fig. 2). Endoscopy of the epispadiac urethra revealed a polypoid lesion on a thin stalk which terminated approximately 2.5 to 3 cm proximal to the meatus and extending along its dorsal wall. Endoscopy of the ventral urethra was normal.

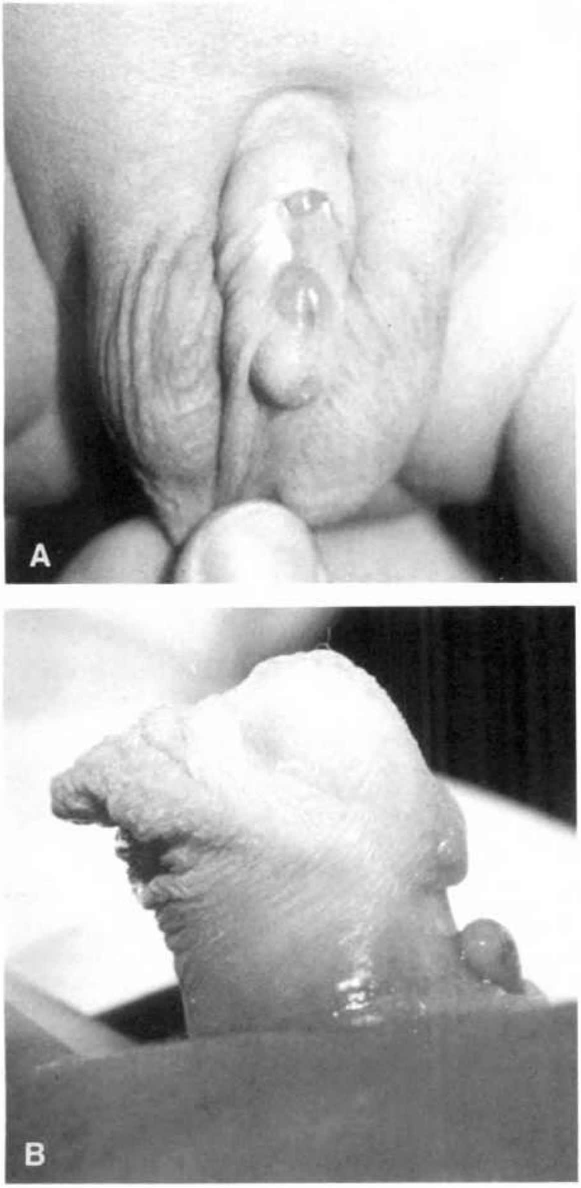

**Fig. 1** (A) View from above and (B) lateral view showing normal urethral meatus, epispadiac urethral meatus with protruding polyp, glanular groove and dorsal chordee.

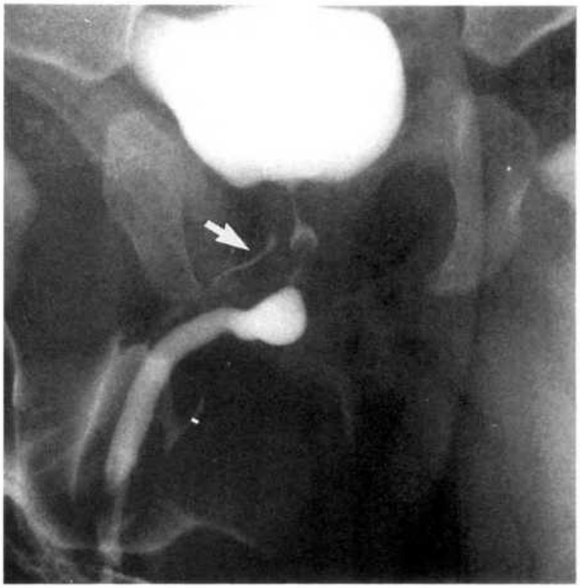

**Fig. 2** Retrograde urethrogram of the epispadiac urethra showing the blind ending.

At the age of 9 months the epispadiac urethra, the polyp and glanular groove were completely excised, the glans was reconstructed and the dorsal chordee corrected. The patient now has a straight penis, a normal glans and voids with complete continence.

## Comment

Congenital urethral polyps, though infrequently reported in the anterior urethra, are, in fact, an anomaly of the posterior urethra extending proximally from the verumontanum. Lou *et al.* (1977) excised, under direct vision, a large urethral polyp extruding from the posterior urethra in an infant with midscrotal hypospadias.

This is the first reported case of a congenital urethral polyp in an epispadiac urethral duplication. Its discovery in the newborn male supports the congenital nature of this lesion. The presence of a urethral polyp in an epispadiac urethra suggests that such a duplication is an integral part of the cloaca which differentiated into the posterior urethra, thereby giving credibility to the theory of Effmann *et al.* (1976) on the aetiology of epispadiac urethral duplications.

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# Chronic Osteomyelitis with Bone Sequestrum Penetrating the Bladder Wall

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## Case Report

A 78-year-old male presented with a 2-month history of painful gross haematuria, increasing urgency and diffuse pain in the lower abdomen. Over a period of 64 years he had suffered from chronic osteomyelitis with consecutive ankylosis of the right hip, the result of an open traumatic injury. Routine blood tests on admission showed a pancytopenia (haemoglobin 6.6 g/dl, leukocytes 2.2 μ/l, thrombocytes 38/μl); urine analysis revealed significant *Pseudomonas* infection. Ultrasound demonstrated an asymmetrical thickened bladder wall on the right side.

Cystoscopy revealed a low capacity bladder with a necrotic area on the right side. After removing necrotic tissue and blood clots, bone contact was felt and a white calcified mass became visible.

A 5-cm bone spur of the osteomyelitic hip, penetrating the bladder wall, was demonstrated by CT scan (Fig.).

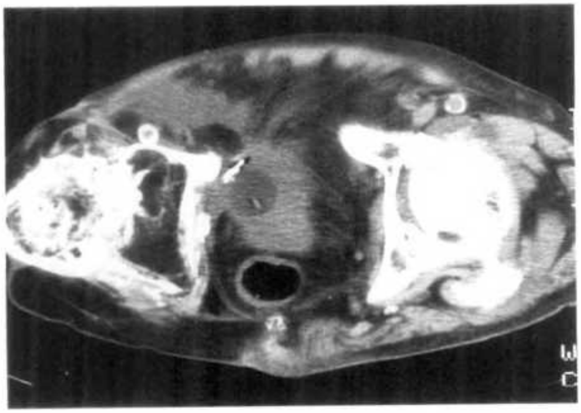

Fig.

Pelvic X-ray revealed a hook-shaped bone sequestrum extending from the right hip to the bladder wall. Treatment consisted of blood transfusions and bladder irrigation with sodium chloride until the urine was clear after 2 days.

## Comment

No report has been found in the literature describing penetration of the bladder wall by a bone sequestrum after trauma caused by chronic osteomyelitis. Becht (1983) reported a case in which methyl metacrylate had penetrated the bladder wall 8 years after implantation of a total hip prosthesis.

The high operative risk caused by the chronic pancytopenia prevented further surgery in this patient.

## Reference

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Requests for reprints to: F. Steinbach, M.D., Klinikum der Johannes Gutenberg-Universität, Langenbeckstrasse 1, 6500 Mainz, Germany.

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# Treatment of Carcinomatous Meningitis from Transitional Cell Carcinoma of the Bladder

D. RAGHAVAN and R. W. M. CHYE, *Urological Cancer Research Unit, Royal Prince Alfred Hospital, Camperdown, Australia*

## Case Report

A 42-year-old male presented with invasive (stage T2, grade III) bladder cancer after a 15-year history of superficial transitional cell carcinoma (TCC) with carcinoma *in situ*, which had been controlled by transurethral diathermy and intravesical chemotherapy in several other centres. He was treated according to a standard protocol with intravenous cisplatin, followed by 60 Gy radiotherapy (Raghavan *et al.*, 1985). Complete remission was achieved, but 16 months later he developed mediastinal lymph node and pulmonary metastases which were confirmed cytologically. He was treated with the combination cytotoxic regimen of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), achieving partial remission after 2 cycles. After the fourth cycle of

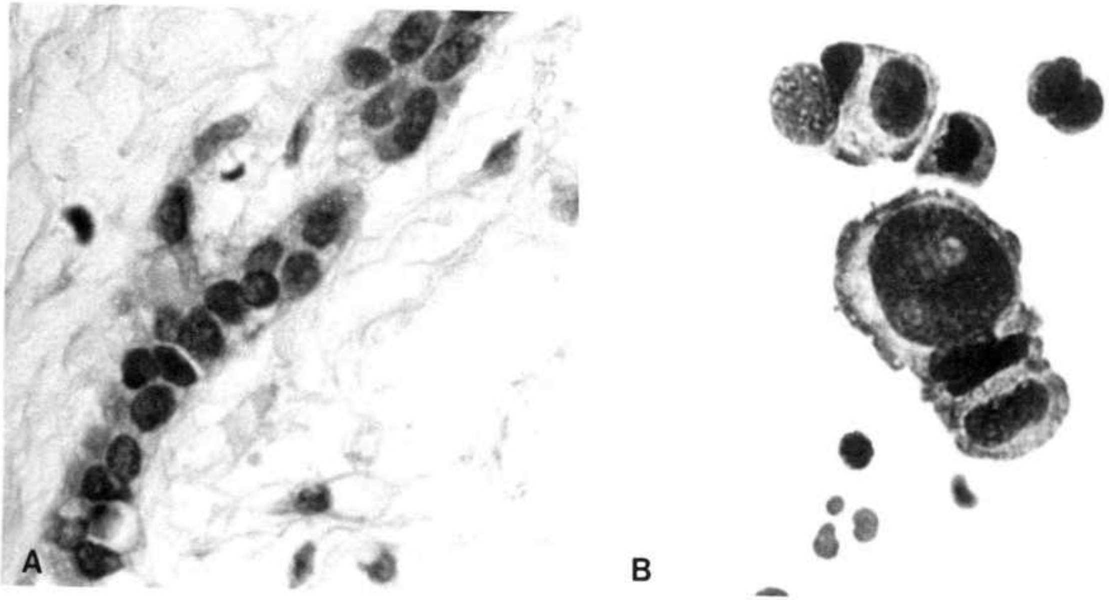

**Fig. 1** (A) Infiltrating transitional cell carcinoma in bladder wall. (H and E × 130). (B) Malignant cells in cerebrospinal fluid (air-dried preparation, May-Grunwald-Giemsa stain). Note resemblance to cells from bladder wall.

treatment he presented with bifrontal, bitemporal headache, drowsiness and mild confusion. There were no localising neurological signs and specifically no clinical evidence of meningism. A computed tomographic brain scan was normal. Spinal tap revealed clear fluid with a pressure of 25 cm $H_2O$, normal glucose and raised CSF protein. Microbiological analysis revealed no infection, but cytology showed clumps of cells with the morphology of transitional cell carcinoma (Figs 1A and B).

An Ommaya reservoir was inserted and intrathecal methotrexate (12 mg per dose) was administered 3 times per week for 6 doses, with complete clearing of the CSF. Methotrexate was then given weekly for another month. In view of his continuing systemic remission, intravenous chemotherapy was also continued to a total of 6 cycles. Four months after presentation with meningeal infiltration the patient developed meningeal relapse, manifested by confusion, mild headache and hiccoughs, with positive CSF cytology. At the same time it was noted that he had developed systemic relapse, with progression of tumour in lungs and liver, and he died 2 weeks later. Autopsy was not performed.

## Comment

We know of only 4 other cases of carcinomatous meningitis arising from bladder cancer (Table), although many cases have been reported in patients with leukaemia, lung cancer and breast cancer (Sorenson *et al.*, 1984). In our review of more than 250 cases of invasive, high grade TCC, this is the first such presentation, representing a prevalence of less than 0.5%. Furthermore, others have shown that positive CSF cytology will be obtained in less than 0.5% of patients with central nervous system

**Table** Patients with Meningeal Metastases from Bladder Cancer

| *Sex* | *Age (years)* | *Stage* | *Grade* | *Clinical syndrome* | *Other sites of metastases* | *Reference* |
|---|---|---|---|---|---|---|
| ? | ? | ? | ? | ? | Cerebrum | Wieczorek (1964) |
| M | 54 | Ta? | II | Disequilibrium, deviation to R. | Nodes* | Hust and Pfitzer (1982) |
| F | 60 | TX | III | Spasticity, ataxia | Nodes, bowel, cerebrum | Hust and Pfitzer (1982) |
| M | 59 | T2 | III | Paraesthesiae, vertigo, diplopia, L. deafness, L. facial nerve paralysis | ? | Mandell *et al.* (1985) |
| M | 42 | T2 | III | Headache, drowsiness, mild confusion | Nodes, lung, bowel | Raghavan and Chye (present study) |

*plus marantic endocarditis.

metastases from bladder cancer (Hust and Pfitzer, 1982).

Despite the rarity of this problem, in a patient with invasive or metastatic bladder cancer with a persistent headache or other central neurological symptoms, accompanied by a normal brain scan, lumbar puncture should be considered in the diagnostic investigations even in the absence of clinical meningism.

Analogous to the management of this problem in patients with leukaemia or breast cancer, we have demonstrated that remission can be achieved through the use of intrathecal methotrexate, with resolution of the neurological syndrome and complete clearing of the cerebrospinal fluid, although only of relatively short duration in this instance. During the time of treatment the patient's quality of life was satisfactory, especially as the use of the Ommaya reservoir replaced the need for repeated lumbar punctures. Mandell *et al.* (1985) have also demonstrated the responsiveness of meningeal TCC to treatment with intrathecal methotrexate, although the duration of remission was not stated; they also treated their patient with craniospinal irradiation, which we chose not to do in view of the associated systemic relapse.

There appears to be a change in the pattern of recurrence in patients treated with chemotherapy for metastatic TCC, with a greater prevalence of metastases to the central nervous system (CNS) (Yagoda, 1988). There will thus be a greater need to develop treatment strategies for these unusual clinical problems, and perhaps even the requirement to consider a role of CNS prophylaxis in patients with high risk disease. However, the features denoting a high risk group for CNS metastases have not yet been specifically defined, and close monitoring for patterns of relapse in treated patients will be required to resolve this issue. Progress in the management of advanced bladder cancer has resulted in the prolongation of survival for many patients, but also in the evolution of new clinical problems. These will only be resolved by a meticulous and structured approach in units with a specific interest in this disease, with careful documentation of their methodology and results.

## Acknowledgements

We are grateful to Dr P. Mackenzie, Department of Anatomical Pathology, Royal Prince Alfred Hospital, for supplying photomicrographs and to Dr J. Blackwood, Consultant Urologist, Western Suburbs Hospital, Sydney, for referring the patient for chemotherapy.

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Requests for reprints to: D. Raghavan, Urological Cancer Research Unit, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia.

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# Pneumoscrotum—an Unusual Complication of Cardiopulmonary Resuscitation

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*Department of General Surgery, Westminster Hospital, London*

Scrotal inflation is a rare condition which may prompt urgent surgical opinion. We report a case which occurred following cardiopulmonary resuscitation (CPR).

## Case Report

A 38-year-old man underwent CPR following a narcotic overdose. He subsequently required mechanical ventilation. Surgical emphysema developed over his neck and a chest radiograph demonstrated air within the mediastinum.

Over 24 h he developed surgical emphysema over this anterior chest wall and a tense swelling of his scrotum (Fig. 1). The swelling was easily compressed without crepitus and readily transilluminated (Fig. 2). Aspiration of air was performed with a fine bore needle and the swelling decreased in size but returned after 6 h. Over the next 72 h the patient's general condition deteriorated and he eventually died.

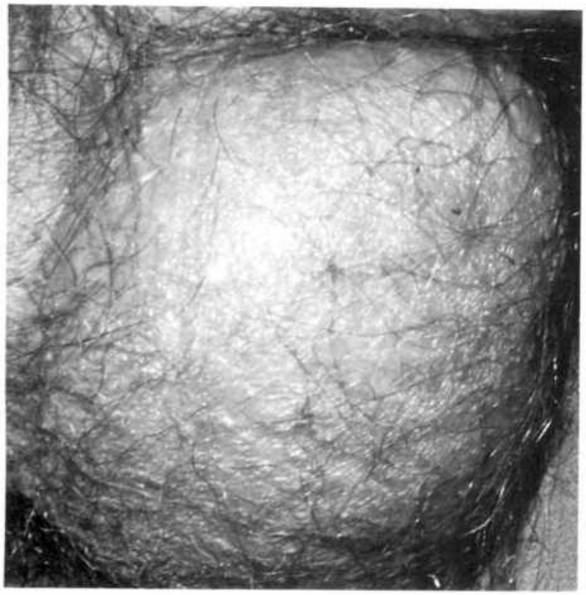

**Fig. 1** Air within the left hemiscrotum.

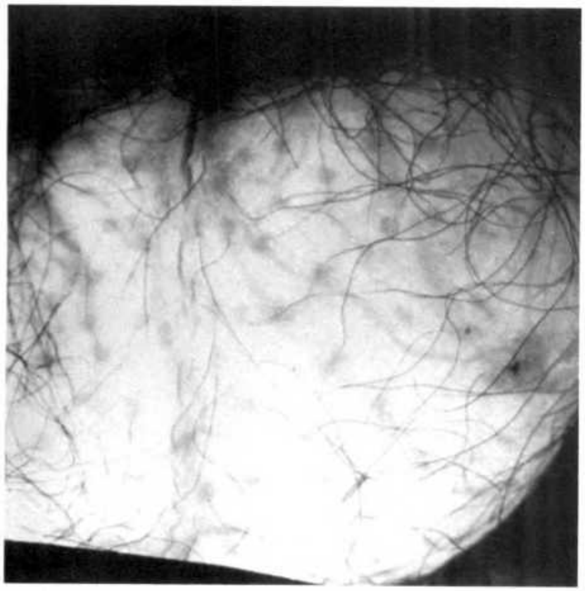

**Fig. 2** Transillumination of the scrotum.

## Comment

Air may reach the scrotum via the peritoneal cavity and a patent processus vaginalis, thus gaining access to the tunica vaginalis. This has been reported following artificial pneumoperitoneum (Christenson *et al.*, 1980). Alternatively, air may enter scrotal tissues via the extraperitoneal tissues of the abdominal wall to end within the subcutaneous tissue of the scrotum. This has been reported following pleural damage, retroperitoneal leakage of air from a duodenal perforation (Castellanos *et al.*, 1973) and anastomotic leakage from bowel resections (Dencker, 1972). This is often termed scrotal emphysema although, unlike classical surgical emphysema, crepitus is rarely demonstrated and a more apt term is pneumoscrotum.

In our patient air entered the mediastinum as a result of CPR and mechanical ventilation. Air then passed from the subcutaneous tissues of the neck, chest and abdominal wall into the scrotum. This case illustrates an unusual complication of CPR and although pneumoscrotum is associated with an alarming clinical appearance, no therapeutic action appears necessary. Should the skin appear threatened, however, repeated aspiration is simple and effective.

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Requests for reprints to: D. Menzies, Department of Surgery, The London Hospital, Whitechapel, London E1 1BB.

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# Radiological Appearances in Prostatic Carcinoma with Rectal Spread

JOSEPHINE BARRY and S. R. WILD, *Department of Radiology, Western General Hospital, Edinburgh*

## Case Reports

*Case 1.* A 68-year-old man presented with altered bowel habit, vomiting and colicky abdominal pain. On examination he had increased bowel sounds and at rectal examination a hard mass was felt encircling the rectum. Sigmoidoscopy confirmed the rectal stricture and biopsies revealed poorly differentiated adenocarcinoma of prostatic origin. A barium enema confirmed the tight rectal stricture. A chest X-ray revealed sclerotic bony metastasis (Fig. 1). Transrectal ultrasound showed almost complete destruction of the prostate with tumour spreading directly to the lower rectum, encircling and thickening its wall (Fig. 2). A bilateral subcapsular orchiectomy was performed with improvement in the patient's symptoms and signs.

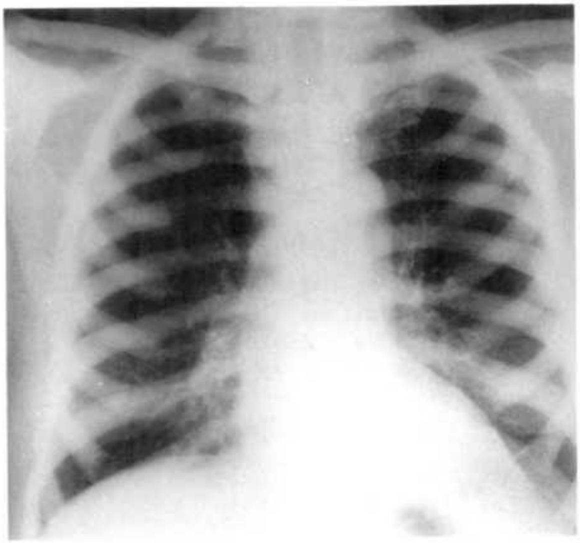

Fig. 1

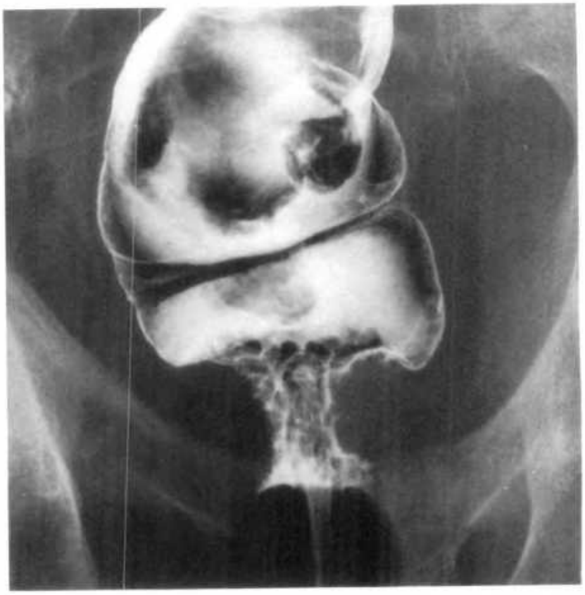

Fig. 3

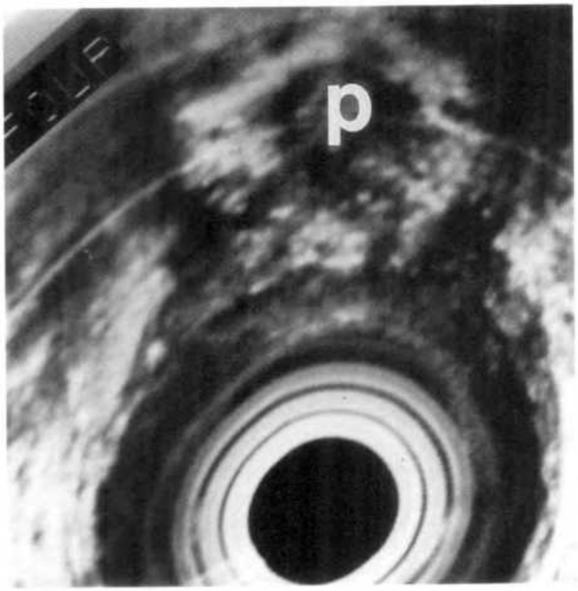

Fig. 2

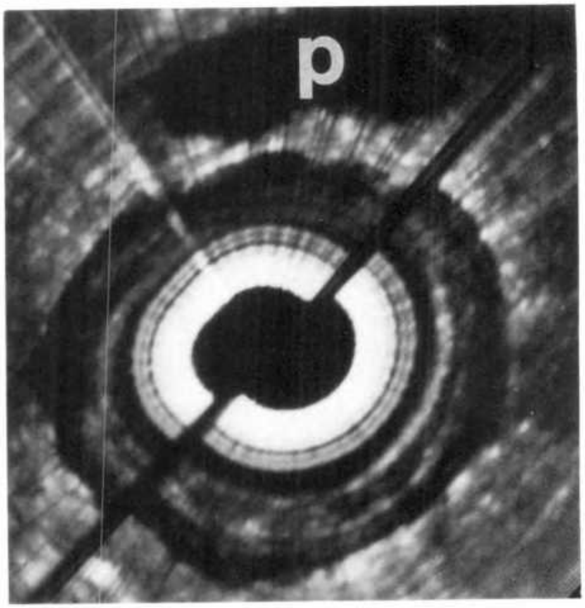

Fig. 4

*Case 2.* A 77-year-old man presented with symptoms of bladder outlet obstruction and a transurethral resection was performed. Histology indicated poorly differentiated adenocarcinoma. Staging revealed sclerotic bone metastasis in several ribs. He underwent a bilateral orchiectomy. Two years later he presented with increasing bone pain and constipation. Rectal examination revealed a tight stricture with mucosal irregularity; rectal biopsies confirmed adenocarcinoma of prostatic origin. Staging was repeated and demonstrated more extensive bony metastasis. A barium enema revealed a 3.5 cm 'apple core' stricture of the rectum (Fig. 3). Transrectal ultrasound demonstrated an irregular margin to the prostate, with thickening of the rectal wall but no continuity between the lesions (Fig. 4). He was treated with palliative external radiotherapy to the prostate and rectum.

## Comment

Spread of prostatic carcinoma to the rectum may occur in up to 10% of advanced cases (Ruggiero and Chang, 1986). This is a manifestation of late disease as the dense fascia which lies between the organs restricts direct spread. The symptoms and signs of rectal extension may mimic a primary rectal tumour but distinction is important, since the management and outcome of both conditions are different.

Direct spread of prostatic tumour to involve the rectum has been demonstrated by CT scanning (Roberts *et al.*, 1985) and magnetic resonance imaging (Phillips *et al.*, 1987). Only 1 of our patients demonstrated direct spread ultrasonically. We postulate that the second case represents a true metastatic deposit, spread having occurred along lymphatic or venous channels.

Transrectal ultrasound offers a useful adjunct to other imaging modalities in demonstrating rectal spread; it is quick and easily repeated and may be particularly useful in assessing tumour response to treatment.

## Acknowledgements

We thank Professor G. D. Chisholm and Dr G. Howard for permission to report these patients. We also thank Mr S. Pye, Medical Physicist, for his help in preparing the images.

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Requests for reprints to: Josephine Barry, Department of Radiology, Falkirk and District Royal Infirmary, Major's Loan, Falkirk FK1 5QE.

*British Journal of Urology* (1991), **67**, 444–445

# Points of Technique

## Radical Urethrectomy in the Female

P. A. HAMILTON STEWART, *Department of Urology, Bradford Royal Infirmary, Bradford*

Unifocal squamous cell carcinoma of the female urethra is an uncommon disease. A radical excision is necessary with an *en bloc* removal of the adjacent bone (Fig. 1).

Synchronous combined abdomino-perineal surgery is advocated. A transverse suprapubic muscle cutting incision is preferred and the retropubic space bluntly dissected. A perineal incision down to bone is made (Fig. 2) with detachment of fascia and origins of muscles from the inferior pubic rami. The obturator foramina are perforated with artery forceps which are used to pull through the Gigli saws on each side. A transverse cut is made through the symphysis, so joining the 2 foramina and another on each side dividing the inferior pubic rami. The bladder is mobilised and separated from the trigone and the superior vesical blood supply is divided unilaterally. The trigone and urethra with surrounding soft tissue and bone are removed. The bladder can then be rotated inferiorly and sutured to the posterior vaginal wall and to the introital skin with absorbable sutures (Fig. 1).

The anterior wall of the vagina is thus reconstructed with an inner surface of peritoneum and the strong muscular wall of the detrusor. The urothelial surface of the bladder is left adherent to muscle. Post-operative examination has shown a healthy spacious vagina.

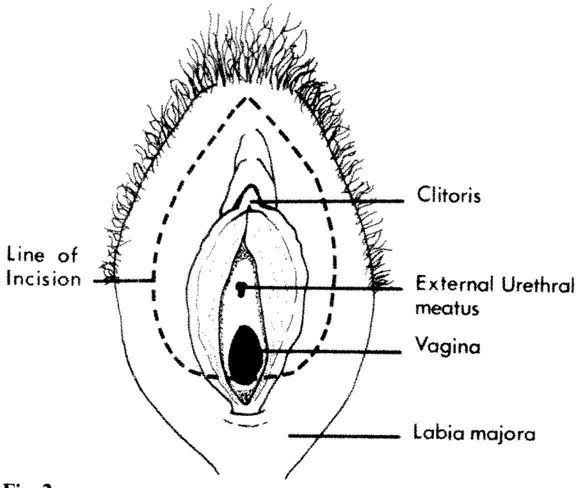

**Fig. 2**

The first part of the operation is similar to that described for radical excision of the male urethra (Shuttleworth and Lloyd-Davies, 1969). In the female, perineal skin closure is impossible. This technique uses the bladder to close the perineal defect and provide tissue for vaginal reconstruction.

### Acknowledgement

Grateful thanks to Carol Fleming, Department of Photography, for the drawings.

### References

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Requests for reprints to: P. A. Hamilton Stewart, Department of Urology, Ward 11 Office, Bradford Royal Infirmary, Duckworth Lane, Bradford BD9 6RJ.

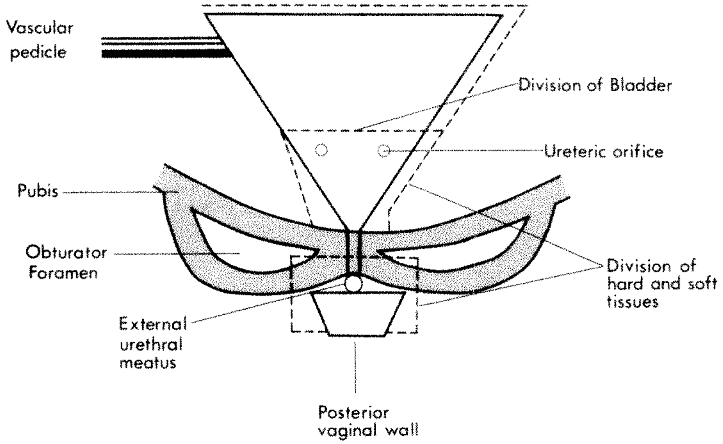

**Fig. 1**

# Repair of Vesicocutaneous Fistula by Rectus Abdominis Myocutaneous Flap

M. W. McDONALD, L. F. ELLIOTT, II, J. W. SULLIVAN and J. ORTENBERG, *Departments of Urology and Plastic Surgery, Louisiana State University School of Medicine, New Orleans, USA*

## Case Report

A 31-year-old male with T4 paraplegia developed a vesicocutaneous fistula after a vesicolithotomy. Intravenous urography showed 2 calculi in a small contracted bladder. Vesicolithotomy and excision of the vesicocutaneous fistula were performed in an operation made difficult by extensive scarring. The vesicocutaneous fistula recurred on the third post-operative day. At re-operation the scar tissue was widely excised to expose the anterior bladder wall and delineate the margins of the bladder defect. A secure 3-layer bladder closure was accomplished. A left rectus abdominis myocutaneous flap based on the left inferior epigastric artery was developed and rotated 90° to fill the defect of skin and subcutaneous tissue left in the suprapubic region following the wide excision of scar (Fig. 1). Urodynamic evaluation demonstrated a reflex neurogenic bladder and a regimen of clean intermittent self-catheterisation and oxybutynin hydrochloride was begun. There has been no recurrence of the fistula 2 years post-operatively (Fig. 2).

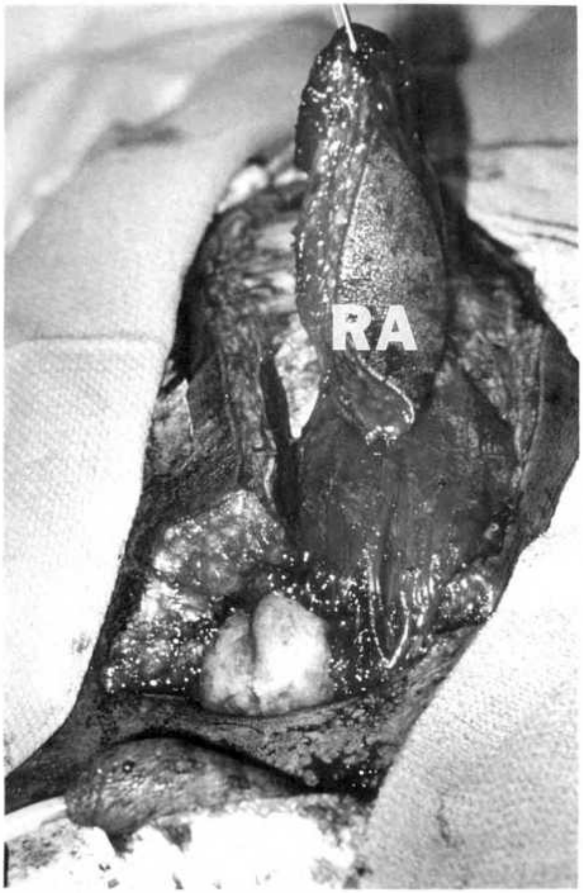

**Fig. 1** Rectus abdominis myocutaneous flap (RA) based on inferior epigastric artery, ready for positioning in suprapubic defect.

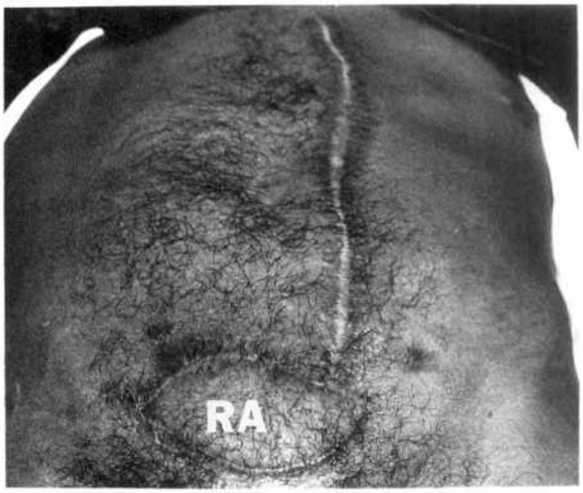

**Fig. 2** Rectus abdominis myocutaneous flap (RA) after healing.

## Comment

Rectus abdominis myocutaneous flaps can be based on the inferior or superior epigastric artery and rotated widely to fill a variety of abdominal wall defects (Mathes and Bostwick, 1977; Bostwick *et al.*, 1979; Heckler *et al.*, 1980). The skin overlying the rectus abdominis is supplied by perforating branches and remains well vascularised. The posterior rectus sheath is left undisturbed and the anterior sheath can usually be closed primarily; functional defect and abdominal wall weakness are minimal or absent.

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Requests for reprints to: M. W. McDonald, Department of Urology, West Virginia State University Medical Center, Morgantown, WV, 26506, USA.

British Journal of Urology (1991), 67, 446

# Notices

## British Association of Urological Surgeons

**President:** R. E. Williams, MD, ChM, FRCS, FRCSE

*Annual Meeting: Glasgow. 25–28 June 1991*

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

## Edinburgh Urological Festival

*Edinburgh. 21–23 August 1991*

Further particulars from: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Edinburgh EH4 2XU.

## Shackman Travelling Fellowship 1992

Applications are invited from Medical Practitioners registered in the United Kingdom who are either trainees in Urology or Organ Transplantation or Consultant Urological Surgeons or Consultant Surgeons with a major commitment to transplantation of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1991.

Further particulars and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

British Journal of Urology (1991), 67, 447–448

# Diary

1991

| | |
|---|---|
| April 4–6 | Senior Registrars' Meeting (SURG), Cambridge. Contact: Mr I Eardley, Dept of Urology, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ. Tel: 0223 245151. |
| April 4–5 | Annual Meeting and Teaching Course—Urological Computing Society. Contact: Lindsay Morrison, Membership Secretary, Urological Computing Society, Southern General Hospital, Glasgow, G51 4TF. |
| April 8–28 | Short Courses in Urology and Nephrology including: The Management of Benign and Malignant Prostatic Disease, Paediatric Urology, The Management of Urological Cancers, Tropical Diseases and GU Medicine, Reconstructive Surgery. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| April 24–28 | 1991 Duke Urologic Assembly. St Thomas, US Virgin Islands. Contact: Linda Mace, Assembly Coordinator, Box 3707, Duke Medical Center, Durham, NC 27710, USA. |
| April 26 | Bradford Urology Symposium. Bradford Royal Infirmary. Contact: Mr G. M. Flannigan, Bradford Royal Infirmary, Bradford BD9 6RJ. |
| April 12–13 | Second Meeting of European Society of Paediatric Urology, Beaune, France. "Neurogenic Bladder in Children and Adolescents". Contact: Dr P. Mouriquand, "Le Dizenier", 11 Impasse Mouillard, 69009 Lyon, France. |
| April 14–19 | Forty-fourth Annual Scientific Meeting of the Urological Society of Australasia, Sheraton Mirage Hotel, Gold Coast, Queensland, Australia. Contact: G. Holmes, President, Brisbane Urology Clinic, 11th Floor, 149 Wickham Terrace, Brisbane, QLD 4000. |
| April 19 | VIIth Symposium of Paediatric Urology, Warsaw, Poland. Contact: Professor A. Borówka, Department of Urology, Medical High School, Lindleya str. 4, 02-005 Warsaw, Poland. Tel: 28 18 96. |
| May 3–4 | Third International Meeting of Andrology<br>Non-surgical Treatment of Impotence. Rome, Italy. Contact: Dr R. Vanzetti, MEDICON ITALIA srl, Piazza Mancini, 4, 00196 Rome, Italy. |
| May 10–12 | XI Athenian Days of Urology 1991, Athens, Greece. Contact: Professor C. Dimopoulos, University of Athens, Laiko Hospital, Goudi-Athens, Greece. |
| May 30–31 | Surgical Andrology, St Bartholomew's Hospital, London. Contact: BAUS Office. |
| May 25–26 | Fifty-sixth Congress of the Societe Belge d'Urologie, Brussels, Belgium. Contact: F. F. Wart, C.H.U.–I.M.C.A.G., Division of Urology, Bd Zoe Drion, 1, B.6.000 Charleroi–Belgium. |

| | |
|---|---|
| June 2–6 | American Urological Association, Metro Toronto Convention Centre, Toronto, Canada. |
| June 7–8 | Fourth Pediatric Surgery Research Workshop, Berlin, Germany. Contact: Dr F. Schier, Pediatric Surgery, Univ.-Klinikum Steglitz, Hindernburgdamm 30, 1000 Berlin 45, Germany. Tel: (0 30) 7 98 41 81/29 09. |
| June 12–15 | Congress of the Portuguese Association of Urology. Funchal, Madeira Island. Contact: Dr Manuel Mendes Silva, Rua Consiglieri Pedrosa, 123, 2745 Queluz, Portugal. Tel: (351-1) 4354044/9. |
| June 16–20 | Canadian Urological Association Annual Meeting, Ottowa. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6. |
| June 17–22 | Diploma Course Revision Block. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| June 18–22 | Tenth World Congress for Sexology, Amsterdam, The Netherlands. Contact: Congress Secretariat, 10th World Congress for Sexology, c/o RAI Organisatie Bureau Amsterdam bv, Europaplein 12, 1078 GZ Amsterdam, The Netherlands. |
| June 25–28 | BAUS Annual Meeting, Scottish Exhibition and Conference Centre, Glasgow. Contact: BAUS office. |
| July 2–3 | Diploma Course Examination. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| August 21–23 | Edinburgh Urological Festival. Contact: Urological Festival Secretary, Department of Surgery/Urology, Western General Hospital, Crewe Rd, Edinburgh EH4 2XU. |
| August 25–31 | First Urology Summer Forum, Oosterbeek. Contact: Secretariat Organization, PO Box 226, 3830 AE LEUSDEN, The Netherlands. |
| September 1–6 | 6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96. |
| September 4–7 | Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllői ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016. |
| September 16–19 | Second Beijing International Symposium on Recent Advances in Urology, Beijing, China. Contact: Gu Fang-liu, Institute of Urology, Beijing Medical University, 1 Da Hong Luo Chang, West District, Beijing 100034, China. |
| September 26–27 | Annual Paediatric Urology Course, Selwyn College, Cambridge. Contact: Mr R H Whitaker, Dept. of Urology, Addenbrooke's Hospital, Cambridge. Tel: 0223 216344. |
| October 4–5 | Autumn Meeting, Royal Surrey County Hospital, Guildford. Contact: BAUS Office. |
| October 9–12 | 1st International Congress, Dutch Urological Association (NVU), Rotterdam. Contact: NVU/PACIOU Congress Secretariat, Department of Urology, Erasmus University Rotterdam/Academic Hospital Dijkzigt, P.O. Box 1738, 3000 DR Rotterdam. The Netherlands. |

# BRITISH JOURNAL OF UROLOGY

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REVIEW

# Lasers in the Treatment of Bladder Cancer

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Although there is persuasive evidence that lasers can successfully eradicate bladder tumours, there is still justifiable scepticism about their clinical application. Significant benefits of laser therapies over cheaper conventional treatment of bladder cancer can only be demonstrated by proper comparative studies. Unfortunately, after more than a decade of research, reports of such studies are noticeably scarce.

A treatise on the physical properties underlying Light Amplification by Stimulated Emission of Radiation is beyond the remit of this article. The reader is directed to the lucid account given by Stein and Kendall (1984). In summary, a laser consists of a laser medium confined between parallel mirrors (Fig. 1). Particles within the medium are raised to a higher energy level by "pumping" in energy from a high power source. In the excited state a particle is unstable and will return to the resting state with the release of energy in the form of a photon (Fig. 2A). In stimulated emission, this photon release is itself precipitated by the impact of a photon. Both the impacting photon and the emitted photon are discharged together and are identical in frequency and phase (Fig. 2B). The process can be repeated in a chain reaction to produce amplification of light to very high energy levels. In a laser the emitted photons are trapped by 2 parallel mirrors and are reflected between them. Amplification occurs and the beam of coherent light so produced is released as a laser beam via an adjustable aperture in one of the mirrors.

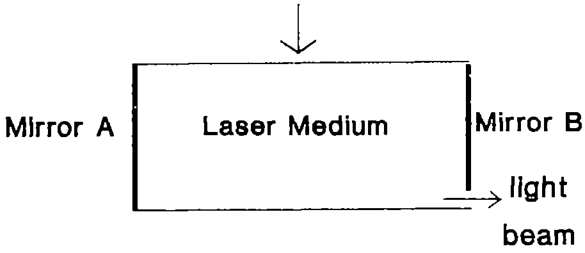

**Fig. 1** Energy is "pumped" from a high powered source into the laser medium Mirror A is totally reflecting. The laser beam emerges through an aperture in the partially reflecting mirror B.

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A laser beam has 3 important properties which result from the way it is generated. It is monochromatic, *i.e.* of a single wavelength dependent upon the type of laser medium. It is coherent (in phase) and since only the light totally reflected between the parallel mirrors is amplified there is little divergence of the beam. An enormous amount of power can therefore be focused into a tiny area, providing very high power densities at the point of action.

Four types of laser are readily available for surgical use (Table). Because the tissue absorption of energy from a particular type of laser depends upon its wavelength, the surgical effects of each of these are quite distinct. To produce effects below the tissue surface, a significant fraction of the laser energy must be transmitted onward into the tissue mass as "forward scatter". Energy reflected from ("back scatter") or absorbed close to the tissue surface is not available for deep penetration.

The carbon dioxide laser produces light of a wavelength which is very strongly absorbed by water. When it hits tissue its energy is quickly dissipated by vaporising intracellular water and the depth of penetration is limited to less than 0.5 mm. This very shallow surface effect has proved inappropriate in the treatment of solid tumours. Water absorption is also a serious drawback for endoscopic work and these factors, together with the lack of a

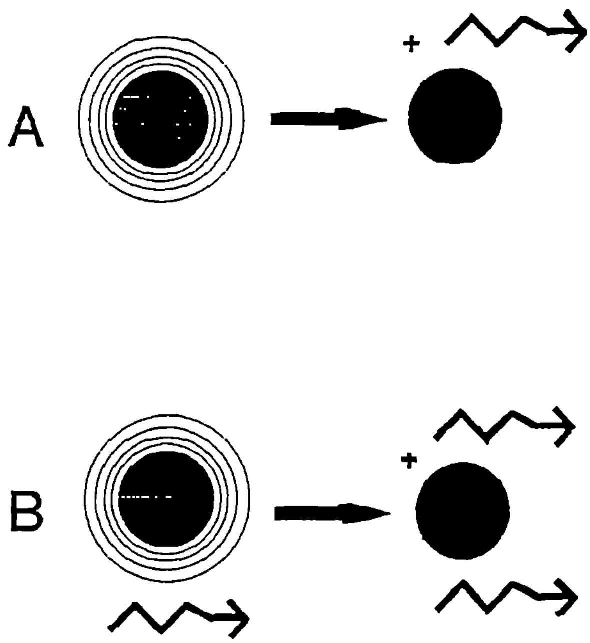

Fig. 2 (A) Spontaneous emission of radiation: An unstable "excited" atom returns to a lower energy state with the emission of a photon. (B) Stimulated emission of radiation: a photon incident upon an unstable "excited" atom stimulates emission of a second identical photon.

suitable fibre to deliver the laser endoscopically, have, until now, effectively prevented the use of the carbon dioxide laser in the treatment of bladder neoplasia.

The argon laser can be directed via a fine quartz fibre and is minimally absorbed by water. It can therefore be applied quite successfully in an endoscopic system. However, this laser light is very strongly absorbed by natural pigments such as haemoglobin. The result is again a rather superficial zone of tissue destruction. There are isolated reports of the use of the argon laser in solid tumours and carcinoma *in situ* but these do not seem to demonstrate any convincing benefit over more accepted treatments, although it does have the advantage of being suitable for use with the flexible cystoscope, thus rendering out-patient treatment of bladder cancers practicable (Biserte *et al.*, 1989).

**Table** Surgical Lasers

| *Laser medium* | *Wavelength (nm)* |
|---|---|
| Carbon dioxide | 10,600 |
| Tuneable dye | 250–700 |
| Argon | 458–515 |
| Nd:YAG | 1064 |

Two types of laser have been used in bladder cancer with rather more promising results. These lasers, the Neodymium: Yttrium Aluminium Garnet (Nd:YAG) laser and the tuneable dye laser, are used to produce tumour necrosis in quite distinct ways. The Nd:YAG works by causing thermal damage to the tissue while the tuneable dye laser is used to photo-activate cytotoxic chemicals in photodynamic therapy. Both lasers are poorly absorbed by water and can be transmitted through fine quartz fibres which pass conveniently through an endoscope.

## Neodymium:YAG Laser

When the beam of an Nd:YAG laser hits tissue, some 30 to 40% of the incident energy is reflected as "back scatter" but a considerable proportion of it penetrates deeply before it is dissipated as heat. The rise in tissue temperature which results depends upon the power density of the beam where it hits the tissue, upon the time for which the laser is activated and upon the rate at which heat is dissipated into the surrounding tissues. In the treatment of bladder cancer the intention is to raise the temperature of the tissue under treatment to between 45 and 60°C at a maximum depth of approximately 0.5 cm. At this temperature cell death occurs due to denaturation of essential intracellular proteins. The temperature is insufficient to boil intracellular water, so that cell walls remain intact. The gross architecture of the tissue persists, although the cells which compose it are dead. This laser "cooking" of tissue is associated with a visible whitening of the tissues. Laser-treated tissue may even be sufficiently preserved to allow a reasonable level of histological interpretation.

For endoscopic surgery to bladder tumours, the laser beam of the Nd:YAG is conducted through a quartz fibre of between 0.4 and 0.6 mm diameter. The fibre passes easily down the instrument channel of the cystoscope and can be directed with a modified Albarran lever as described by Hofstetter and Frank (1979). Alternatively, direct aiming is possible using a fibreoptic cystoscope (Fowler, 1987). The Nd:YAG laser itself is invisible, being of a wavelength in the infrared range (1064 nm). The instrument is therefore equipped with a helium-neon pilot laser which shines a red spot on the target. The tip of the fibre is held between 0.25 and 0.75 cm distant from the tumour while the laser is activated. The laser is usually fired in short bursts of less than 5 s, while moving the point of application over the surface of the tumour as the visible changes of laser tissue necrosis become apparent.

Some of the earliest and most persistently enthusiastic reports of the use of the Nd:YAG laser in bladder tumours have appeared in descriptions of the pioneering work of Professor A. G. Hofstetter and his colleagues (Staehler and Hofstetter, 1979; Rothenberger *et al.*, 1983; Hofstetter, 1986).

As a means of producing thermal tissue destruction the Nd:YAG laser competes with surgical diathermy, a relatively cheap and effective modality with a long and honourable history in transurethral resection and coagulation of bladder tumours. A number of theoretical advantages of the laser are advanced by its proponents as arguments for its use in place of diathermy.

The fact that tissue destruction occurs without touch has been put forward as one of the major theoretical advantages of Nd:YAG surgery over conventional techniques. It is argued that the dispersion of viable cells into the irrigant and their subsequent implantation are important factors in the generation of recurrent bladder tumours, a view for which there is some indirect and some experimental evidence (Weldon and Soloway, 1975; Page *et al.*, 1978). If this is indeed the case, there ought to be a reduced incidence of recurrent tumours after "no touch" Nd:YAG laser surgery, which should not cause cell dispersion.

Hofstetter (1986) maintained that a "no touch" method was also less likely to be associated with intramural lymphatic dispersion of tumour cells. He advocated a preliminary "sealing" of lymphatics by a circumferential laser burn encircling the tumour and argued that this was an important part of his treatment protocol. This contention is supported by the fact that the spread of ink particles through the lymphatics of the rat bladder wall can indeed be limited by a zone of laser coagulation (Zimmerman *et al.*, 1984).

On the face of it these theoretical claims seem impressive. However, it seems quite possible that equally good lymphatic sealing could be achieved by similar circumferential coagulation with the ball diathermy. Such a precaution might be sensible before transurethral surgery on a tumour were there not a suspicion that spontaneous lymphatic dispersion of cells in an active muscular organ like the bladder is likely to exceed the effect of surgical manipulations. What is more, the advantages in both intramural and intracellular dispersion are negated with most new bladder tumours whose diameter exceeds 1 cm. Because the depth of penetration of the Nd:YAG laser is limited to 0.5 cm, large tumours must be treated in the first instance by transurethral resection. The laser is used at a second sitting to coagulate the base of the tumour when any intraluminal tumour spread will already have occurred.

Keiditsch (1981) claimed that the necrosis produced by the Nd:YAG laser was more uniform than that resulting from diathermy coagulation. In a histological comparison of tissue destruction, he was able to show that the laser produced a zone of homogeneous necrosis when it acted on the bladder wall. By comparison, the diathermy coagulation was irregular and less well demarcated from untreated tissue. It was suggested that there were cells within the zone of diathermy coagulation which escaped destruction due to preferential electrical conduction along structures such as blood vessels. The existence of viable cells within treated tissue is of great theoretical importance where the intention is to eradicate tumour infiltrating deep into the bladder wall by coagulation alone. However, in practice, the effect is unlikely to be of importance in superficial tumours or in diathermy resection where tissue is physically removed. Furthermore, the depth and reliability of prolonged ball diathermy coagulation are not reported and further studies in this area would seem appropriate.

Conventional endoscopic management of superficial bladder tumours is associated with a recurrence rate of 60% or more (England *et al.*, 1981). If this rate were significantly reduced by one or all of these factors there would be good grounds for the use of the Nd:YAG laser. Early reports of uncontrolled and short-term studies gave cause for optimism (Staehler and Hofstetter, 1979; Okada *et al.*, 1982). However, after almost 10 years, it has to be acknowledged that this effect remains to be demonstrated in an adequately controlled comparison, although the work of Beisland and Seland (1986) should perhaps be excluded from this criticism. More recently, several workers have stated that they are unable to demonstrate a reduced recurrence rate (Smith and Middleton, 1985; Randall and Arkell, 1988) and this is also true of the writers.

The Nd:YAG laser has also been used in the treatment of invasive bladder cancers in small numbers of patients in whom other forms of treatment have been deemed unsuitable. Transurethral resection of the tumour has been followed by extensive laser treatment of the underlying bladder wall in an attempt to eradicate all tumour remaining in it. Although encouraging results have been reported (Hofstetter *et al.*, 1982; Beisland and Saunders, 1990), small numbers and comparatively short follow-up make objective assessment of the technique difficult at present.

An alternative justification of the Nd:YAG laser is that it can be used without the need for general anaesthesia. It is generally agreed that surgical diathermy to the bladder is extremely painful. The Nd:YAG laser treatment causes much less discomfort; thus endoscopic laser surgery under topical urethral anaesthesia is possible and by using the laser with the fibreoptic cystoscope, bladder tumours can be treated in the out-patient clinic (Fowler, 1987). The laser does not perforate the bladder and produces little bleeding, so that post-operative catheterisation is rarely necessary and the patient can return home immediately after treatment. Whether such methods become accepted is likely to depend upon the cost benefits which can be seen to accrue from a move from in-patient to out-patient treatment. In addition, the potential benefits in terms of patient convenience should not be underestimated.

Besides the high capital cost of the equipment, laser surgery has other disadvantages. Diathermy electrodes are relatively robust and last for hundreds of procedures. By comparison, laser light-guides are temperamental and require frequent polishing. They are also very expensive to replace. Special precautions must be taken when a laser is installed to ensure that all those who may come into contact with it are protected from eye damage. All occupants of the laser room must be equipped with protective goggles, reflective surfaces must be dulled and the doors must be locked and alarmed to prevent the unwary from entering while the laser is in action. Such necessary precautions, which must be applied with unvarying rigidity, can be irksome to staff used to the convenient and familiar diathermy machine.

The main clinical disadvantage of the Nd:YAG laser is the occasional perforation of bowel that has been damaged by its proximity to the bladder wall while it is being treated with the laser (Kronester *et al.*, 1981). Necrotic bowel is digested by intestinal enzymes, resulting in perforation which may occur up to 72 h after laser treatment to the bladder. Pensel *et al.* (1981), using a thermocamera, showed that the risk of dangerously high temperatures outside the bladder was reduced if the power setting of the laser was limited to 40W. However, prolonged laser action even at this setting may lead to thermal damage beyond the bladder wall. Because it is not possible to measure the depth of the thermal effect during surgery, the surgeon must use his judgement in limiting the power output of the device and the time for which the laser acts upon a particular site. It is usual to limit the pulse duration to 5 s, the maximum output to 40W and to move the point of action of the laser over the target as if painting it with light. With these precautions, the incidence of this serious complication is very low (Hofstetter, 1986).

## Photodynamic Therapy

In photodynamic therapy light energy is not used to create a thermal effect but instead is used to initiate a photochemical reaction. That some chemicals could react with light to have a toxic effect on unicellular organisms has been known since the turn of the century (Raab, 1900). The tumour localising properties of systemically administered porphyrins was documented in the 1940s (Figge *et al.*, 1948) and in 1961 Lipson *et al.* developed a derivative of haematoporphyrin and used its fluorescent properties for tumour localisation. Haematoporphyrin derivative has been widely used in experimental and clinical work since then.

The mechanism of tumour localisation has been proven over the last 20 years to be less specific than originally suggested. It probably depends upon several tissue factors resulting in delayed clearance of the drug rather than on actual tumour take-up (Bugelski *et al.*, 1981). However, haematoporphyrin derivative is known to be transported in the blood stream carried on lipoproteins and since some tumours have receptors for low density lipoproteins it seems reasonable to postulate that this is a method of tumour localisation of the photosensitiser (Barel *et al.*, 1986).

That tissue damage can occur from photoactivation of the porphyrins is apparent in the cutaneous photosensitivity which is a feature of some of the naturally occurring porphyrias. Lipson *et al.* (1967) demonstrated that the photosensitising properties of haematoporphyrin derivative might be used to inhibit tumours and in 1972 Diamond *et al.* used photodynamic therapy to kill gliomas that had been implanted in rats.

The mode of action of photodynamic therapy is not completely understood. It is thought to depend on the production of singlet oxygen by the photosensitiser on exposure to light, and the subsequent reaction of the singlet oxygen with membrane bound enzyme systems resulting in loss of integrity of the cell membrane and thus cell disruption (Weishaupt *et al.*, 1976; Valenzo, 1987).

Although all of the early experimental work on photodynamic therapy was done using very powerful white light sources with filters to remove the unwanted wavelengths, the use of the tuneable dye laser has allowed much more efficient activation of the photosensitiser. It produces light over a range of wavelengths depending on the dye used, and can be "tuned" to remove all but the precise wavelength needed to activate the photosensitiser. Haematoporphyrin derivative, in common with the other porphyrins, can be activated at several different wavelengths; 630 nm is used clinically as it has reasonable tissue penetration.

Photodynamic therapy has enormous theoretical advantages in the treatment of bladder cancer. It relies on there being differential retention of photosensitiser in the tumour compared to the surrounding tissues 4 to 36 h after intravenous injection. This introduces a degree of tumour selectivity far in excess of other treatments such as chemotherapy and radiotherapy. High concentrations of light can easily be delivered into the bladder by passing the laser light-guide transurethrally. The light can be diffused to allow the whole of the bladder to be illuminated at one sitting by altering the shape of the bulb at the end of the laser fibre or by filling the bladder with a fatty emulsion which diffuses the light (Baghdassian *et al.*, 1985). Alternatively, areas of neoplasia may be treated focally.

The first clinical report of the use of haematoporphyrin derivative in bladder malignancy was by Kelly and Snell in 1976. They demonstrated porphyrin fluorescence in both flat and exophytic tumours after systemic administration of haematoporphyrin derivative. A single case of bladder cancer treated by photodynamic therapy was reported by Kelly *et al.* (1975), since when there have been many clinical studies (Benson *et al.*, 1983; Hizazumi *et al.*, 1983). The results of photodynamic therapy in 20 patients were described in a collaborative study between the United States and the People's Republic of China (Prout *et al.*, 1987).

The effects of photodynamic therapy on the bladder are now well documented. Initially, before lasers became available for photodynamic therapy, tumours were treated focally as whole bladder illumination would have been an extremely lengthy and complicated affair. The results of focal treatment were very good; small tumours were completely destroyed and even larger ones (<2 cm) were partially destroyed (Hizazumi *et al.*, 1983).

However, if the whole bladder is treated, patients experience a severe desquamating cystitis almost immediately following illumination of the sensitised bladder. When the bladder is assessed at follow-up cystoscopy several weeks after treatment the inflammatory change has usually subsided and most studies show good remission of superficial exophytic tumours within the treated field. Although the initial inflammation subsides, illumination of the sensitised bladder wall results in destruction of normal tissues and their replacement with fibrous tissue. This results in an alarmingly high incidence of reduced bladder capacity which may be associated with upper tract dilatation (Harty *et al.*, 1989). Invasive tumours are not treated because of the limited penetration (0.5 cm) of the light through the bladder wall.

Haematoporphyrin derivative is retained in the skin and as a result patients suffer from severe cutaneous photosensitivity and must stay out of direct sunlight for 4 to 6 weeks after treatment.

Such side effects are particularly important in a disease where recurrence is common and in the absence of any evidence that photodynamic therapy reduces the rate at which they occur, more conventional means of treating superficial exophytic tumours are preferable at present.

Because photodynamic therapy can be used to treat the whole bladder, it lends itself to the treatment of carcinoma *in situ*. In this condition, lesions may be focal or widespread and may be difficult to identify visually. A treatment acting in a wholesale manner against all neoplastic disease while sparing normal urothelium clearly proffers an advantage. Photodynamic therapy has been used to locate and treat carcinoma *in situ* (Benson *et al.*, 1983) and it seems that histological remission of the disease can be expected for at least a few months after treatment. Unfortunately, recurrences occur and although comparative trials are not available, the overall effectiveness of photodynamic therapy does not seem to exceed that of conventional treatments.

In a few patients with severe malignant cystitis, the symptoms may be markedly reduced by whole bladder photodynamic therapy in spite of the subsequent reduction in bladder capacity and these patients probably represent those for whom this treatment is appropriate at the moment.

Haematoporphyrin derivative obviously has several drawbacks in clinical use. It is a complex mixture, largely consisting of materials that are inactive *in vitro* (Berenbaum *et al.*, 1982), with a composition that varies between batches in an uncontrollable fashion. The wavelength that gives greatest tissue penetration (the Soret band) is one of the least efficient of the excitatory wavelengths for haematoporphyrin derivative. Also, most importantly, haematoporphyrin derivative causes marked skin photosensitivity and also sensitises normal tissues to such a degree as to render photodynamic therapy unsuitable for many clinical situations. An attempt has been made to overcome these problems by the use of photofrin II, a preparation of haematoporphyrin derivative that is enriched in di-haematopophyrin ester, thought to be the active portion of haematoporphyrin. Unfortunately, this material shares the main disadvantages of haematoporphyrin derivative, it has an incompletely defined composition and weak excitation by the red waveband.

A new generation of photosensitisers is being developed to overcome these problems. Three main groups of drugs show promise; the meso-tetra (hydroxyphenyl) porphyrins, the chlorins and the phthalocyanines. These drugs are chemically pure; they are strongly activated by red light and it is hoped that their increased potency will result in a therapeutic difference between the levels of photosensitiser in normal and malignant tissue, allowing safe and effective treatment of tumours. The availability of new photosensitising agents with much greater tumour specificity would totally change the outlook for photodynamic therapy.

The specialised equipment needed will restrict the use of photodynamic therapy to specialist centres but there may be a case for its use in those patients with multiple superficial recurrences or with carcinoma *in situ*, in whom it may well obviate the need for radical surgery.

A question mark remains over the place of lasers in the treatment of bladder cancer. There are lingering doubts whether the Nd:YAG laser treatment has significant clinical benefits over conventional thermal means of endoscopic tumour destruction. Photodynamic therapy is associated with pronounced side effects and its future in the treatment of bladder cancer will depend on the development of photosensitisers that have higher tumour specificity.

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# Urinary Retention after Pyeloplasty

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Summary—A retrospective review of 37 pyeloplasties, performed between 1984 and 1988, revealed that 38% of patients had post-operative retention requiring catheterisation, compared with 8% in an age and sex matched group of patients undergoing cholecystectomy. This suggests that direct surgical trauma to the upper genitourinary system may inhibit bladder function. We therefore suggest that pre-operative catheterisation should be considered in theatre, for patients undergoing pyeloplasty.

Urinary retention after major abdominal surgery is a common post-operative complication. Stallard and Prescott (1988) reported that 23% of patients (n = 70) undergoing laparotomy required post-operative catheterisation and Davies *et al.* (1989) found it necessary in 48% of patients (n = 64) undergoing nephrectomy. To date, it has not been our policy routinely to catheterise patients before pyeloplasty.

In order to ascertain whether the increased incidence of urinary retention was a direct result of nephrectomy or due instead to surgery performed on the upper urinary tract, we have studied post-operative catheterisation in patients undergoing pyeloplasty.

## Patients and Methods

The records of 37 patients treated by pyeloplasty between 1984 and 1988 were reviewed. There were 18 males and 19 females with a mean age of 30 years (range 15–65). Table 1 shows the incision used for pyeloplasty and Table 2 shows the type of external/internal drainage used. Prophylactic antibiotics were administered only when operating on potentially infected patients. Initial post-operative analgesia was given in the form of an intramuscular opiate.

The following details were obtained from the medical and nursing notes: duration of the procedure, use of diuretics and intravenous fluids, time of insertion of catheter, duration of insertion, complications during catheterisation and results of urine culture on removal of the catheter.

A control group of sex and age matched patients undergoing cholecystectomy was obtained retrospectively from the results of a weekly audit. The cholecystectomies were performed via a midline or transverse incision.

**Table 1** Type of Incision in Pyeloplasty Patients and Percentage Requiring Catheterisation

| *Incision* | *No. of patients* | *No. catheterised (%)* |
|---|---|---|
| Anterior (extraperitoneal) | 27 | 12 (44) |
| Loin | 10 | 2 (20) |
| Total | 37 | 14 (38) |

Anterior vs loin $\chi^2 = 3.04$, $P > 0.05$.

**Table 2** Incidence of Catheterisation in Relation to Drainage Techniques

| *Drainage* | *No. of patients* | *No. catheterised (%)* |
|---|---|---|
| None | 25 | 11 (44) |
| Cummings | 7 | 1 (14) |
| "J" stent | 5 | 2 (40) |

None vs Cummings $\chi^2 = 3.52$, $P > 0.05$.
None vs "J" stent $\chi^2 = 0.43$, $P > 0.5$.

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## Results

Of the 37 patients undergoing pyeloplasty, 14 (38%) required post-operative catheterisation (Table 1). The effect of external/internal drainage in relation to post-operative catheterisation is shown in Table 2. The overall incidence of post-operative catheterisation was 39% in the male patients and 37% in the females. All catheterisations were performed within 24 h of surgery and in each case more than 450 ml of urine were drained from the bladder. The mean length of time the catheter remained *in situ* was 3 days (range 1–4). The mean operating time for pyeloplasty was 1.5 h (range 1–3) and for cholecystectomy it was 1 h (range 0.5–2). These times were estimated to the nearest 15 min. In the pyeloplasty group requiring catheterisation the mean operating time was 1.5 h (range 1–3) and in the non-catheterisation group it was also 1.5 h (range 1–2.5). All pyeloplasty and control patients were receiving intravenous fluids at the time of catheterisation.

There were no complications attributable to urethral trauma. Urinary infection (*i.e.* organisms $>10^5$) was found in 4 patients prior to catheter removal; 15 patients (43%) had > 100 pus cells with no organisms in the specimen.

Of the 37 control patients undergoing cholecystectomy, 3 (8%) needed post-operative catheterisation. Yates' correction was applied to compare the incidence of catheterisation in these 2 groups and the results were statistically significant ($P<0.001$, $\chi^2=10.996$).

## Discussion

The number of pyeloplasty patients who required post-operative catheterisation was greater than expected despite our earlier finding that 48% of patients undergoing nephrectomy required catheterisation (Davies *et al.*, 1989). The pyeloplasty patients were younger than those undergoing nephrectomy and this supports the view that factors other than outflow obstruction must be responsible. In the present study there was no difference in post-operative catheterisation rates between the sexes. The type of incision and the use of external drainage did influence the rate of post-operative catheterisation. A possible explanation for the latter may be a form of partial defunctioning which allows a longer time to elapse before maximum bladder capacity is reached.

The use of drugs such as atropine (Taira, 1972) and opiates (Petersen *et al.*, 1982) during the peri-operative period may influence micturition. Fluid intake and balance are important, but in a retrospective study it was not possible to ascertain exactly when each patient micturated prior to surgery. All patients received intravenous fluids both peri-operatively and at the time of catheterisation. None received diuretics in the peri-operative phase up to the time of catheterisation. The influence of these factors should be similar in both the pyeloplasty and control groups. However, 2 other factors that may have contributed to the problem are lack of privacy and the difficulty of micturating in the supine position. Nevertheless, these factors do not explain the higher incidence of catheterisation following pyeloplasty. These results, if summated with those from our previous study (Davies *et al.*, 1989), show an incidence of post-operative catheterisation in renal surgery of 45% ($n=101$) compared with 16% in the control group ($n=101$) ($P<0.001$, $\chi^2=19.75$).

What is the reason for this difference? In most respects there was no significant difference between the pyeloplasty and control groups. Even though pyeloplasty was a slightly longer procedure, there was no difference within this group for mean procedure time in the retention and non-retention patients. Direct trauma to the upper genitourinary system may influence bladder function in the post-operative period, a phenomenon which may be analogous to the post-operative ileus seen after manipulation of the bowel.

The fact that the ureters have a large number of sensory fibres may be relevant (Warwick and Williams, 1989). It is possible that trauma to the ureter initiates a local reflex arc or induces a central response which results in the inhibition of bladder emptying. Before any further neurological explanation can be suggested, an experimental model will be required.

Complications were encountered in 4 patients who developed bacteriuria and 15 who had more than 100 pus cells/field. However, the results reported by Haskell *et al.* (1974) suggest that an even lower rate of bacteriuria would be obtained if catheterisation were performed in theatre. Furthermore, the length of time the catheter is *in situ* has been shown to be important (Givens and Wenzel, 1980; Sethia *et al.*, 1987). The results of both this study and our earlier one (Davies *et al.*, 1989) suggest that consideration should be given to peri-operative catheterisation in patients undergoing renal surgery.

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# Assessment of Tumour-infiltrating Lymphocytes, Regional Lymph Node Lymphocytes and Peripheral Blood Lymphocytes and their Reaction to Interferon-gamma in Patients with Renal Carcinoma

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Summary—The immunological distribution of tumour-infiltrating lymphocytes (TIL), regional lymph node lymphocytes (RLNL) and peripheral blood lymphocytes (PBL) was evaluated by means of immunohistochemical staining using monoclonal antibodies of each subset of lymphocytes (stored in frozen sections) in a series of 22 patients with renal carcinoma. The immunological effect of IFN (interferon)-gamma on these immunocompetent cells was also investigated. The effect of IFN-gamma on TIL was an increase in CD3 (pan-T cells), especially an increase in CD8 (cytotoxic/suppressor-T cells). When examining these cells according to stage and grade, a marked increase in CD3 was found in low stage and low grade patients. With regard to RLNL, there was a tendency towards a decrease in CD3 and an increase in CD20 (B-cells) following the administration of IFN-gamma. No specific effect on stage and grade was observed apart from a reduction in T cell subset ratios in high grade patients. With regard to PBL, no specific trend was noted except for an increase in CD16 (NK cells) when IFN-gamma was administered.

Renal carcinoma is one of the most difficult malignant urological tumours to cure, the main reason being that no effective treatment (other than surgery) has been established (Keane *et al.*, 1990). However, evidence of improvement in the efficacy of treatment can be seen when immunotherapy based on interferon is applied clinically, although it is less effective when used alone (Horoszewicz and Murphy, 1989). This is because it is difficult to assess the immunological efficacy of IFN with particular reference to the renal tumour itself. It is also difficult to detect the immunological environment surrounding it on the basis of changes in immunocompetent cells in the peripheral blood alone (Stenzl and deKernion, 1989). Thus we have investigated the population of tumour-infiltrating lymphocytes and regional lymph node lymphocytes, using immunohistochemical methods and peripheral blood lymphocytes in terms of the effect of IFN-gamma on cell-mediated immunity in renal carcinoma by comparing 2 groups of patients: the first group received nephrectomy alone and the second received IFN-gamma pre-operatively.

## Patients and Methods

We studied 22 patients with renal carcinoma who had undergone radical nephrectomy at Jikei University Hospital. They were divided into 2 groups: the first (12 patients) were not given IFN-gamma pre-operatively (untreated group) and the second group (10 patients) did receive IFN-gamma pre-operatively (treated group). Their clinical background is shown in Table 1. They were also divided into a low stage group (stages 1 and 2) and a high stage group (stages 3 and 4). A similar system was used for grades: low grade (I and II) and high grade

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**Table 1** Details of Patients

| | No | Pt. | Age (years) | Sex | Side | Stage | Grade | Lymph node metastasis | Survival (alive) | Complications |
|---|---|---|---|---|---|---|---|---|---|---|
| Patients not treated with IFN-gamma | 1 | T.K. | 55 | M | L | 2 | II | – | 1 yr 1 mon | — |
| | 2 | S.W | 52 | F | R | 1 | II | – | 1 yr 1 mon | — |
| | 3 | F.O | 61 | F | R | 2 | III | – | 1 yr | — |
| | 4 | S.S. | 47 | M | R | 1 | II | – | 9 mons | Chronic renal failure (dialysis patient) |
| | 5 | H.J. | 56 | M | L | 2 | II | – | 9 mons | — |
| | 6 | T U. | 64 | M | L | 2 | I | – | 9 mons | — |
| | 7 | T.N. | 70 | F | L | 3B | I | + | 7 mons | — |
| | 8 | F.K. | 79 | M | L | 3A | III | – | 5 mons | — |
| | 9 | S.Y. | 57 | M | L | 3A | III | – | 5 mons | — |
| | 10 | S.Y. | 61 | M | L | 1 | II | – | 4 mons | — |
| | 11 | H.F. | 55 | F | L | 1 | I | – | 3 mons | — |
| | 12 | E.N. | 61 | F | L | 4B | II | – | 2 mons | — |
| Median age=57 years. Sex ratio M: F=7.5. Affected side L. R=9:3 Low stage. high stage=8:4. Low grade: high grade=9:3. | | | | | | | | | | |
| Patients treated with IFN-gamma | 1 | K.S. | 41 | M | R | 1 | I | – | 1 yr | — |
| | 2 | K.H. | 51 | F | R | 2 | II | – | 1 yr | — |
| | 3 | O S. | 60 | M | R | 4B | III | + | 10 mons | — |
| | 4 | I.O. | 52 | M | L | 2 | II | – | 8 mons | — |
| | 5 | H.N. | 45 | M | L | 1 | II | – | 7 mons | — |
| | 6 | T K. | 57 | M | R | 2 | II | – | 6 mons | Accompanied by stomach cancer |
| | 7 | T.I. | 73 | M | R | 4B | II | – | 6 mons | — |
| | 8 | K.K. | 46 | M | R | 2 | I | – | 4 mons | — |
| | 9 | F S. | 52 | M | L | 2 | III | – | 4 mons | — |
| | 10 | K.N | 63 | M | R | 3A | III | – | 3 mons | — |

Median age=52 years. Sex ratio M: F=9.1. Affected side L: R=3:7. Low stage: high stage=7.3. Low grade: high grade=7:3.

(III and IV). No bias was found between the patients with regard to stage and grade.

### Administration of IFN-gamma

IFN-gamma (nHuIFN-gamma) was administered daily (intramuscularly) in a dose of $3 \times 10^6$ iu (mean total dose: $2.1 \times 10^7$ iu) from 6 to 11 days prior to surgery (average 7). All patients experienced side effects such as fever, general fatigue and anorexia, but they were not severe enough to prevent nephrectomy.

### Immunological evaluation

With regard to the primary tumour ($3 \times 3$ cm) we focused on the peripheral portion which contained normal tissue. The lymph nodes were halved and using one half as the specimen, the rest was subjected to pathological examination. The specimens were placed in trays filled with OCT, quick-frozen in dry ice-acetone for approximately 1 min and then subjected to immunological staining (Table 2).

Using the cluster of differentiation classification (Kurrle *et al.*, 1989), we investigated the lymphocyte subsets CD3 (pan-T cells), CD4 (helper/inducer-T cells), CD8 (cytotoxic/suppressor-T cells), CD16 (NK cells: natural killer cells) and CD20 (B cells). In the case of PBL, we examined the lymphocyte subsets by means of flow cytometry.

### Analysis of tissue specimens

After preparing the specimens according to the procedure shown in Table 2, we photographed each lymphocyte subset consecutively in the same field, calculated the area of positive cell groups for each subset using an image analyser (Nexus 6000) and personal computer. After calculating the area of negative control cell groups (all nucleated cells) occupying the entire field, we determined the ratio of positive lymphocyte subset cells to nucleated cells in the same field.

### Items investigated

We investigated the difference between the untreated and treated groups with respect to the following items:

(1) TIL distribution pattern and the effect of

**Table 2** Immunohistochemical Staining Methods

| | |
|---|---|
| Step 1 | (Freeze-embedding): $4\sim6$ μm thinly sliced frozen sections prepared in a cryostat were placed on albumen-coated glass slides. |
| Step 2 | (Section drying, washing): After air-drying for 30 min at room temperature, and after washing 3 times for 5 min each time in cold PBS and treatment with endoperoxidase inhibitor, the specimen was washed 3 times, 5 min each time, with cold PBS. |
| Step 3 | (Blocking non-specific reactions): The sections were treated with 10% unsensitised serum (normal sheep serum) for 20 min at room temperature and lightly rinsed with PBS |
| Step 4 | (Primary antibody reaction): The first antibody (monoclonal antibody) was placed on the sections with a capillary pipette and reacted in a moisture chamber at 37°C for 1 h |
| Step 5 | (Washing): It was then washed 5 times or more for 5 min each time with cold PBS. |
| Step 6 | (Enzyme-labelled anti-mouse antibody reaction)· Reacted with HRP (horseradish peroxidase) labelled secondary antibody at 37°C for 1 h in the moisture chamber. |
| Step 7 | (Washing): It was then washed 5 times or more, 5 min each time, with cold PBS. |
| Step 8 | (DBA colouration). Reacted with $DBA\text{-}H_2O_2$ solution (3,3′-diaminobenzidine), to which 10 mM sodium azide had been added, for 5 min at room temperature. |
| Step 9 | (Washing): After washing 3 times, 5 min each time, in cold PBS, it was rinsed twice with distilled water. |
| Step 10 | (Nuclear staining): After-stained for 1 h with 4% methyl green solution. |
| Step 11 | (Dehydration, enclosure): Ethanol dehydration, transparent sealing in xylol, microscopic examination. |

IFN-gamma administration on the ratio of each subset.

(2) RLNL distribution pattern and the effect of IFN-gamma administration on the ratio of each subset.

(3) Effect of IFN-gamma on the ratio of each PBL subset.

(4) Effect of IFN-gamma according to stage and grade.

Classification of the staging system was proposed by Robson *et al.* (1969) and the grading system was divided into the 4-step method (Bannayan and Lamm, 1980). The Z test was used to evaluate the differences in mean values for the 2 groups.

## Results

### *TIL distribution pattern and the effect of IFN-gamma on the ratio of each subset*

In an attempt to identify the distribution patterns in the untreated group, the following observations were made: 7 patients had the diffuse pattern (*i.e.* lymphocyte infiltration was scattered throughout the tissue), 4 patients had the focal pattern (lymphocyte infiltration in clusters) and 1 patient had a combination of both patterns.

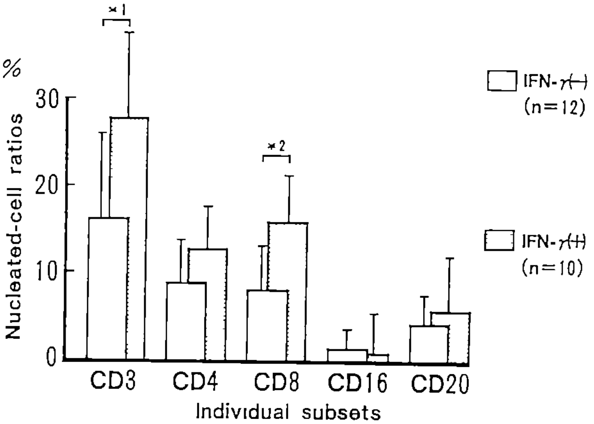
In the treated group, the diffuse pattern was observed in 8 patients, the focal pattern in 1 and the mixed pattern in 1 patient.

To calculate the mean ± SD of the ratios for each lymphocyte subset from all nucleated cells (negative control) in the untreated and treated groups, we compared them within each group. In the treated group there were significantly higher ratios for CD3 and CD8 and a significantly lower CD4/CD8 ratio subsequently (CD3: $P<0.01$; CD8: $P<0.02$; CD4/CD8 ratio: $P<0.05$) (Fig. 1).

### *RLNL distribution pattern and the effect of IFN-gamma administration on the ratio of each subset*

Identification of the distribution patterns within the untreated group with regard to CD3 revealed that 10 patients had the diffuse pattern and 1 had the mixed pattern. For CD20, the focal pattern was found in 10 patients, the diffuse pattern was not detected, and the mixed pattern was found in 2 patients. No lymphocyte infiltration was observed within the metastatic foci, but infiltration of CD3 (focal pattern) and CD20 (focal pattern) was observed surrounding the foci.

On examining the treated group with regard to CD3, we found 7 patients had the diffuse pattern, 2 had the focal and 1 had the mixed pattern. With regard to CD20, there were 9 patients with the focal and 1 with the diffuse pattern. Patients with regional



*1: $P<0.01$, confidence coefficient=3 806, Z=2.6064
*2· $P<0.02$, confidence coefficient=3.0902, Z=3.1043

**Fig. 1** TIL subset ratios with and without IFN-gamma

lymph node metastases showed no difference in the pattern of infiltration when compared with the untreated group. Thus no specific effect was observed between the patients undergoing nephrectomy alone and those receiving pre-operative IFN-gamma with respect to RLNL infiltration patterns.

Comparison of the mean ±SD of each lymphocyte subset from all nucleated cells in the untreated and treated groups showed that CD3 and CD4 were lower in the group treated with IFN-gamma, but the differences were not statistically significant. An increase in CD20 was observed, however, and this difference was significant (Fig. 2).

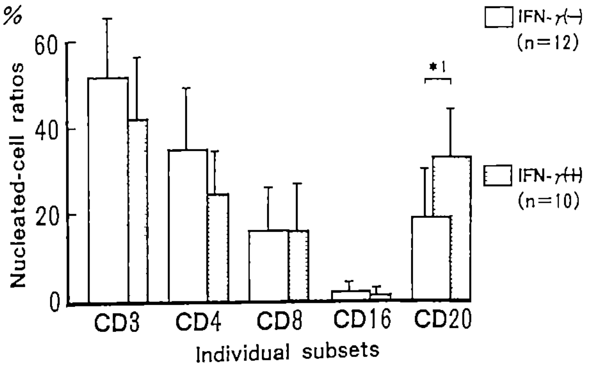
### *Effect of IFN-gamma on the ratio of each PBL subset*

When we compared the mean ±SD of each lymphocyte subset in both groups and its value in the treated group before administration of IFN-gamma, we found a significant rise in CD16 ($P<0.03$) in the treated group (20.1±5.4%) compared with levels before administration (13.9±7.0%) ($P<0.03$).

### *Effect of IFN-gamma according to stage and grade*

In calculating the subsets of the TIL according to stage, we found a tendency for subset ratios to be higher in the high stage patients in the untreated group (Fig. 3).

Assessment of the effect of IFN-gamma on low stage patients showed that CD3 and CD8 were significantly higher in patients treated with IFN-gamma (CD3: $P<0.004$; CD8: $P<0.03$) (Fig. 3). When we examined the high stage patients, although there was a tendency towards increases in CD3 and CD8, no significant difference was observed between the untreated and treated groups (Fig. 3).



*1: $P<0.04$ confidence coefficient=2.0537, Z=2.1476

Fig. 2 RLNL subset ratios with and without IFN-gamma.

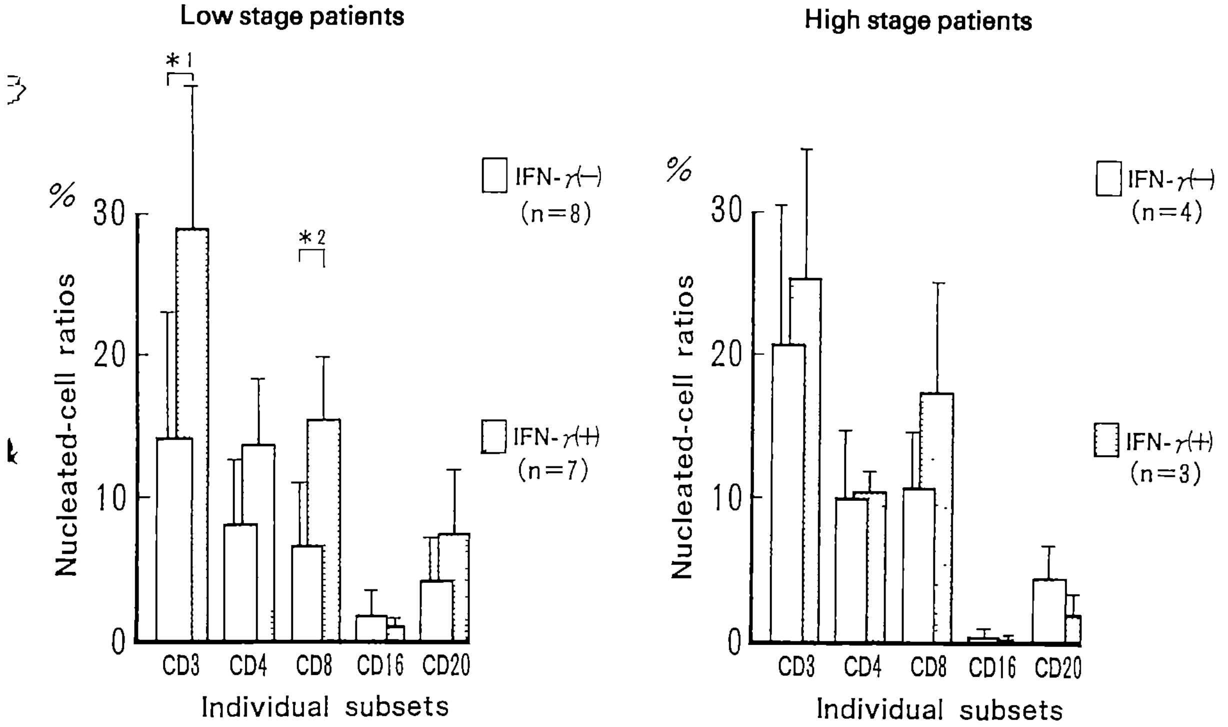
As to the subsets of the TIL according to grade, no significant differences were observed in the untreated group. When we examined the effect of IFN-gamma we found a significant elevation in CD3 and CD8 among the low grade patients (CD3: $P<0.004$; CD8: $P<0.05$) (Fig. 4). In the high grade patients no significant effect of IFN-gamma was detected (Fig. 4).

We compared the mean ±SD of the RLNL subset ratios with respect to stage and grade regardless of whether or not IFN-gamma had been administered. Comparison of the overall ratios of the subsets between the low stage and high stage patients in the untreated group revealed that the subset ratio of CD3, CD8 and CD20 tended to be higher in the low stage patients. No significant difference was observed between the groups with or without IFN-gamma (Fig. 5). Furthermore, when we compared low grade and high grade patients in the untreated group, no significant difference was found. When we examined the effect of IFN-gamma, no significant changes were detected in low grade patients (Fig. 6). In high grade patients a significant decrease in CD3, CD4, CD8 and CD16 was observed in the treated group (CD3: $P<0.03$; CD4: $P<0.0001$; CD8: $P<0.0001$; CD16: $P<0.02$) (Fig. 6).

Examination of PBL showed a significant increase in CD16 alone following administration of IFN-gamma, with no correlation between stage and grade.

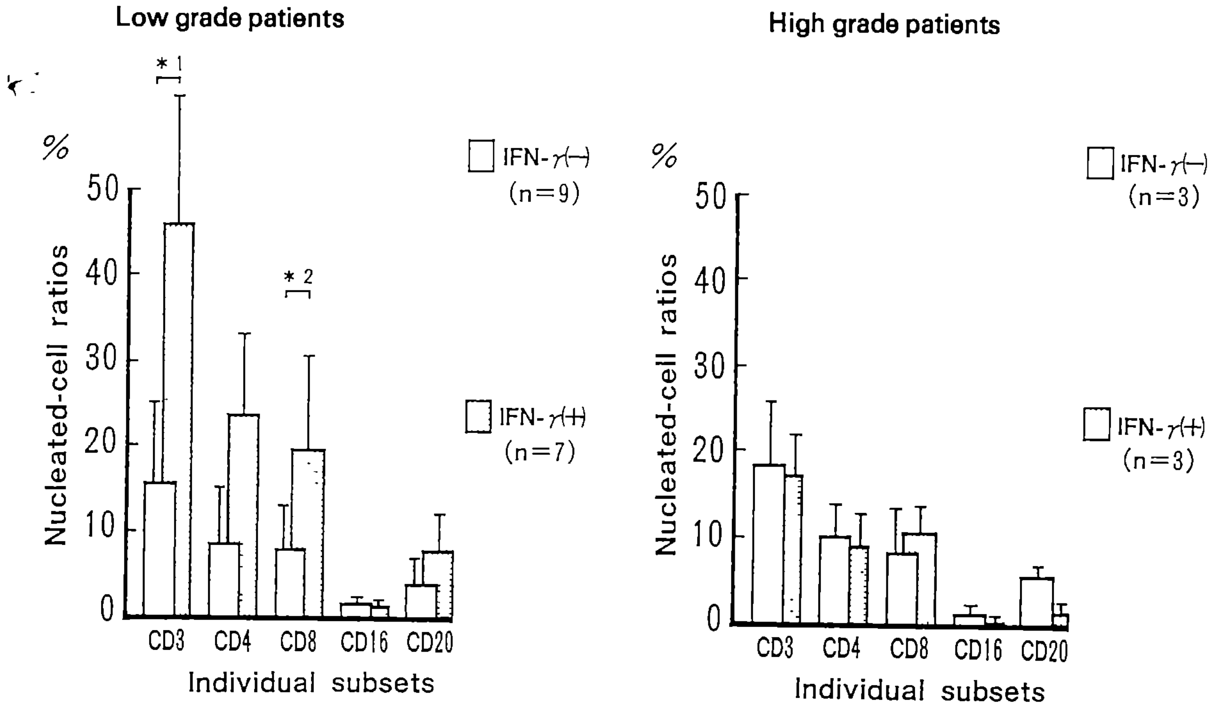
## Discussion

As far as the immunological effects of IFN-gamma are concerned, the effects mediated by the host's immune system in addition to direct effects have been described. With regard to the former, the effects have included macrophage activation, potentiated effect of NK cell activity, modulation of LAK (lymphokine activated killer) activity, and antibody-dependent cell-mediated cytotoxicity (ADCC) (Hengst *et al.*, 1983). No definite conclusion has been drawn concerning the minimum dose of IFN which produces changes in the immune system. As far as can be seen from monocyte antitumour activity *in vitro*, based on a report that excessive administration of IFN reduced antitumour activity (Kleinerman *et al.* 1986), there appears to be an optimal dose of IFN. The results of the present study and a report by Kurzrock *et al.* (1986) have confirmed an increase in PBL and NK



*1: $P<0.004$, confidence coefficient = 2.8751, Z = 2.8862
*2 $P<0.003$, confidence coefficient = 3.6156, Z = 3.6708

**Fig. 3** Effect of IFN-gamma on TIL according to stage (low stage and high stage).



*1: $P<0.004$, confidence coefficient = 2.0537, Z = 2.1088
*2: $P<0.05$, confidence coefficient = 1.9600, Z = 1.9820

**Fig. 4** Effect of IFN-gamma on TIL according to grade (low grade and high grade).

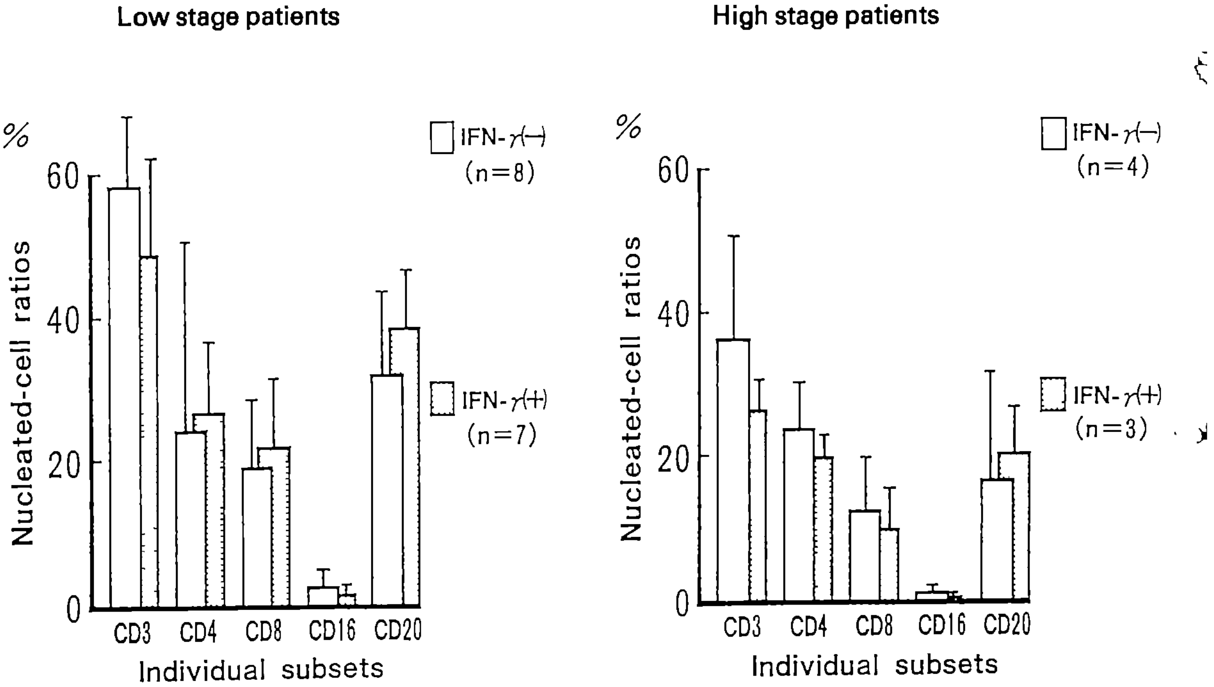
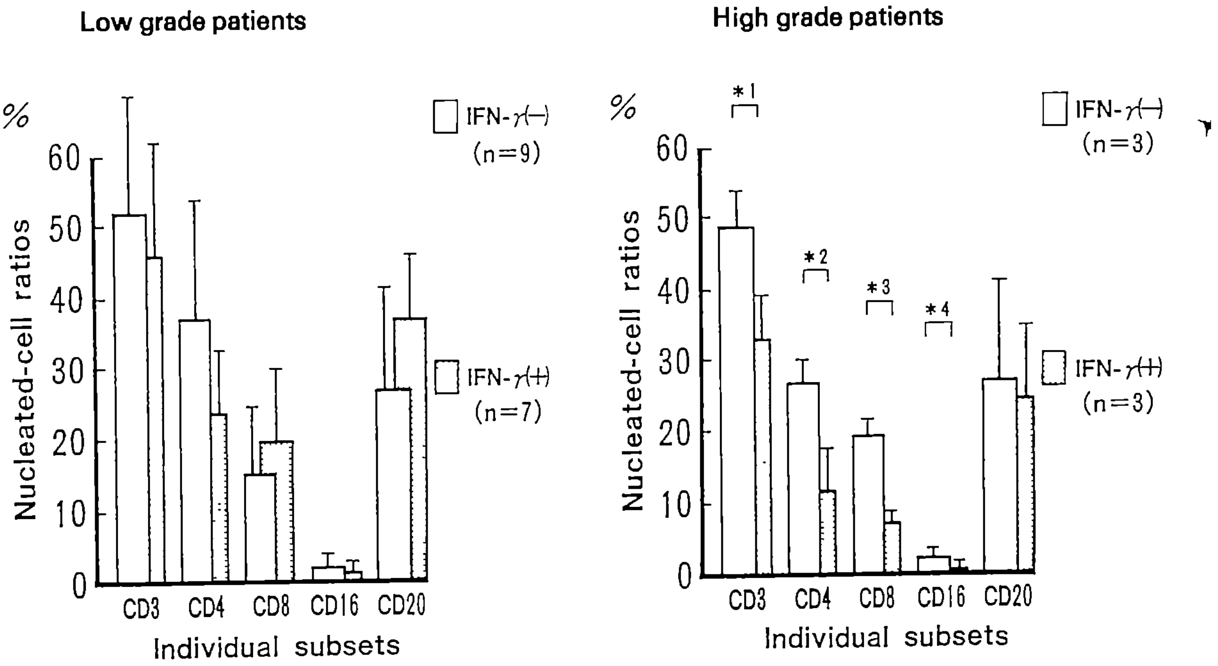


**Fig. 5** Effect of IFN-gamma on RLNL according to stage (low stage and high stage).



*1: $P<0.03$, confidence coefficient=2.9677, Z=3.0806
*2: $P<0.0001$, confidence coefficient=4.203, Z=4.4696
*3: $P<0.0001$, confidence coefficient=3.8913, Z=6.3901
*4: $P<0.02$, confidence coefficient=2.3263, Z=2.3540

**Fig. 6** Effect of IFN-gamma on RLNL according to grade (low grade and high grade).

cells in response to an average 3- to 7-day administration of IFN-gamma. Hence, it appears that the host's immune system is altered relatively soon after the administration of IFN-gamma.

### *Effect of IFN-gamma on TIL pattern and the distribution of its subpopulations*

A study of lymphocyte infiltration of malignant lesions by Mims *et al.* (1966) revealed considerable lymphocyte infiltration in the primary lesion with spontaneous regression of bony metastasis; this resembled the histological findings in rejection of transplanted kidneys. Grumstedt and Wahlquist (1969) reported that renal carcinoma patients with round cell infiltration in the peripheral area of the tumour had a good survival rate. Matsuda *et al.* (1976) classified the degree of lymphocyte infiltration in renal carcinoma into 3 grades, with a tendency towards a better prognosis in patients with the highest degree of infiltration. The findings in these studies (Mims *et al.*, 1966; Grumstedt *et al.*, 1969; Matsuda *et al.*, 1976) make the investigation of tumour-infiltrating lymphocytes of considerable interest, especially when related to prognosis. However, these reports were concerned only with mononuclear cell infiltration, and no work has been carried out on the character of mononuclear cell infiltration in tumours and the patterns of distribution.

As far as the pattern of CD3 (T-cell) infiltration in renal carcinoma is concerned, it is clear that in many patients this was diffuse. With regard to TIL, in contrast to the composition of the subsets of PBL, more than half were T-cells, and in addition to these, a portion comprised B-cells, whereas very few NK cells were observed. Hardly any NK cells are found in TIL subpopulations according to Nakamura *et al.* (1988) in their study of lung carcinoma patients, and Hurlimann and Saraga (1985) in their study of breast carcinoma patients. These reports confirm our findings.

Hiratsuka *et al.* (1984), in a study of 17 patients with oral carcinoma, investigated the subsets of TIL using immunohistochemical staining. They noted that 14 of 17 patients had a considerable degree of CD3 infiltration and that the pattern of infiltration was focal or diffuse within the tumour, or it surrounded the periphery. This resembled the pattern of CD3 infiltration in TIL of renal carcinoma. With regard to the proportion of the TIL subset within CD3, there was no definite tendency in CD4 and CD8 subset ratios, and these subset ratios approximated the TIL subsets of the untreated patients in the present study. However, in a report on the proportion of TIL subsets in malignant melanoma (Ruiter *et al.*, 1982), there was significantly greater infiltration by CD8 than by CD4, and it is assumed that there are also differences in the ratios of the TIL subsets depending on the type of cancer.

From the standpoint of the function of these tumour-infiltrating T-lymphocyte subpopulations, a high correlation between the degree of TIL and tumour antigenicity was shown in an experiment using rat autologous tumours by Kikuchi *et al.* (1976), where approximately 75% of the infiltrating lymphocytes in high antigenic tumours were composed of T and B cells, and two-thirds of them were CD8. It is presumed, therefore, that the lymphocytes which participate in rejecting tumour cells, *i.e.* tumours exhibiting strong antigenicity, are CD8 (cytotoxic/suppressor-T cells).

With regard to the subsets of TIL, a significant increase in CD3 positive cells and CD8 positive cells was observed in patients treated with IFN-gamma. This finding, together with the results reported by Kikuchi *et al.* (1976), suggest that IFN-gamma enhances the antigenicity of renal carcinoma.

### *Effect of IFN-gamma on RLNL infiltrating pattern and subpopulations*

Many factors concerning the immunological assessment of regional lymph nodes in cancer remain unresolved even now. It is said that CD3 shows the diffuse pattern in the thymus-dependent area around the lymphoid follicles within the lymph nodes, and CD20 shows the focal pattern in the primary follicles and the mantle zones. There is no difference in these patterns between cancer patients and healthy men (Hiratsuka *et al.*, 1984).

Analysis of the effects of IFN-gamma revealed a significant increase in CD20 and a decrease in CD3. It may be possible to understand this increase in CD20 among the subsets of RLNL as an increase in the interstitial dendritic cells (IDC), which have an antigen-presenting function under IFN-gamma (Corradi *et al.*, 1987).

### *Effect of IFN-gamma treatment according to stage and grade*

Evaluation of the efficacy of IFN-gamma on TIL in low stage patients showed a marked increase in T cells, especially CD8, so that the immunological effect of IFN-gamma was more marked in the low stage patients. No significant differences were observed between the low grade and high grade patients in the untreated group. In the treated group, however, a significant increase in the subset ratio, *i.e.* T-cells, especially CD8, was observed in low grade patients following administration of IFN-gamma. The efficacy of IFN-gamma on TIL therefore appears to be more marked in the early cancerous stage and in the lower grade patients.

When we investigated RLNL in a similar way, we found no significant differences in the subsets of RLNL according to stage, nor were any effects observed following the administration of IFN-gamma. With regard to grade, however, we found a significant decrease in the subsets of RLNL (except for CD20). These results suggest that the effect of IFN-gamma on RLNL is related to the grade of the primary lesion.

It was concluded that the subsets of TIL and RLNL were different from the subset of PBL. It is hoped that future studies on the functional character of infiltrating lymphocytes will attempt to further the understanding of the essence of cancer immunity. We feel that some light has been shed on the effect of IFN-based immunotherapy on tumour cells and the measures needed to enhance its efficacy.

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# Incontinence in the Elderly: Objective Demonstration and Quantitative Assessment

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Summary—Subjective and objective methods of demonstrating incontinence and assessing its severity have been compared in a group of elderly patients with a high incidence of severe urge incontinence. It was found that 24-h in-patient monitoring of urine leakage was the most sensitive method of demonstrating incontinence, with videourodynamic testing almost as good. In comparison, a 1-h pad test was poor. Visual inspection during physical examination seldom demonstrated leakage. For quantitative assessment of severity, 24-h monitoring gave the most reproducible results; it was also able to reveal significant changes in severity in response to pharmaceutical treatment. A 1-h pad test was less reproducible and suggested changes that were only poorly consistent with 24-h monitoring. The subjective responses of the patients were not useful in assessing changes in the severity of incontinence. Twenty-four hour monitoring thus stands out as a superior method of demonstrating and assessing incontinence.

Two reasons for measuring the amount of urine leaked by apparently incontinent patients are to confirm or exclude a diagnosis of incontinence in doubtful cases and to assess the severity of the incontinence, or changes in severity in response to treatment (I.C.S., 1983, 1988). Severity may be defined as the amount of leakage in a given period and is usually measured by weighing pads worn by the patient while performing prescribed activities (Sutherst *et al.*, 1981; I.C.S., 1983, 1988). How long such a "pad test" should last is controversial. Clearly, the longer the test the more inconvenient it is, but the higher the probability that leakage will actually occur (Mayne and Hilton, 1988) and the more likely it is to give reproducible results. Durations of 40 min to 48 h have been proposed (Jakobsen *et al.*, 1987a). The reproducibility of a 1-h test is debatable (Klarskov and Hald, 1984; Christensen *et al.*, 1986; Lose *et al.*, 1986). Jørgensen *et al.* (1987) suggested that, in mild stress incontinence, a 24-h home-based pad test was both reproducible and more sensitive for detecting incontinence than a 1-h pad test.

To demonstrate incontinence objectively but not quantitatively, observation of leakage during videourodynamic tests is an alternative to a pad test (Stanton, 1984). It is not known which method is the more sensitive. It is possible that physical examination, or the patient's history, might give adequate information without the need for elaborate testing.

We have compared 24-h in-patient monitoring, a 1-h pad test, videourodynamics, physical examination and the patients' histories, as part of a study of incontinence among elderly patients. In this age group, incontinence is frequently severe and mainly of the urge type.

## Patients and Methods

Fifty patients in a geriatric unit (31 females, 19 males, median age 79 years), who were referred with established urinary incontinence, were investigated on an in-patient basis. Written informed consent was obtained from each patient and also

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from the carer if the patient suffered from confusion. Many patients had some cognitive impairment: the median minimental state was 23/30 (Folstein *et al.*, 1975). Most had limited mobility, although none was bedridden: the median score for activities of daily living (Katz *et al.*, 1963) was 3/8. Initial assessments included a medical history and physical examination, a comprehensive incontinence history from the patient (supplemented by the carer if necessary), 24-h incontinence monitoring, a 1-h pad test and provocative videourodynamic testing. An intervention was then instituted. In 39 patients, a short history, 24-h monitoring, a 1-h pad test and videourodynamics were repeated after 2 to 4 weeks. Methods, definitions and units conform to the standards recommended by the International Continence Society (I.C.S., 1988), except where specifically noted.

The incontinence history included questions on frequency of incontinent events, precautions taken and frequency of changes (*e.g.* of pads) and how long voiding could be postponed after the urge to void was felt. For female patients the physical examination included inspection for leakage at rest and during coughing. This was usually done in the supine position because of impaired mobility.

During 24-h monitoring, normal daily hospital activities were carried out. During waking hours, pre-weighed absorbent briefs ("pads") were changed and weighed every 2 h or sooner if obviously saturated. At night the pad was checked every 2 h and changed if damp. We also monitored fluid intake, voiding and residual urine (non-invasively). On the basis of the 24-h monitoring a diagnosis of incontinence was made if 1 or more pads increased in weight by more than 2 g (I.C.S., 1983, 1988). The severity of the incontinence was assessed primarily from the total increase in weight of all of the pads over the 24-h period.

During the 1-h pad test similar pre-weighed briefs were worn. A 1-h schedule similar to that recommended by the International Continence Society (I.C.S., 1988), with modifications to make it easier for older patients, was attempted (Table 1). The severity of the incontinence was assessed from the gain in weight of the pad. A weight gain of more than 2 g indicated significant urine leakage (I.C.S., 1988).

Videourodynamic tests were done in the supine and, whenever possible, sitting positions, using an X-ray-translucent table/chair designed to minimise the physical demands on the patient and to ensure that all urine leakage or voiding took place into a flowmeter. The bladder was filled at a medium rate with room-temperature X-ray contrast medium. Stress testing was performed by asking the patient to cough while recording intravesical, abdominal and detrusor pressures, the fluoroscopic appearance of the urethra and any leakage into the flowmeter. Filling was continued until the patient had a very strong desire to void or, more usually, uninhibited voiding occurred.

**Table 1** Schedule for 1-h Pad Test for Incontinence (simplified from International Continence Society recommendations)

Test is started without patient voiding.

Pre-weighed pad is put on and test begins.

*0–15 min:*

Patient drinks 500 ml sodium-free fluid, sitting or resting.

*15–40 min:*

Patient sits and rests.

*40–60 min.*

Patient performs following activities, as far as possible:
(a) walking for 5 min, including up and down 5 steps
(b) standing up from sitting, 5 times
(c) coughing vigorously, 5 times
(d) bending to pick up small object, from floor if possible, 5 times
(e) washing hands in running water for 1 min

Pad is removed and reweighed.

If the pad becomes saturated during the test it is removed and weighed and replaced by a fresh pre-weighed pad.

In principle the subject should not void during the test. If he/she experiences urgency, then he/she should be persuaded to perform as many of the activities (a)–(e) as possible before voiding. If voiding cannot be postponed then the pad is removed and reweighed and the test terminated.

## Results

Videourodynamics gave objective evidence of urge incontinence in 62% of the patients; 64% stated that they were unable to hold their urine for as long as 10 min after feeling the urge to void. Patients underwent various interventions, but 75% received oxybutinin chloride in doses from 5 mg at bed-time to 5 mg *tid*. A regular toilet regime and/or evening fluid restriction were also frequently recommended. Two men with urge incontinence were found to have significant urethral obstruction and were referred to a urologist.

In 4 patients, no pre-intervention test demonstrated any urine leakage. Two of these patients denied incontinence, despite the perception of the referring physician. In the other 2 cases post-intervention 24-h monitoring showed slight leakage.

Prior to intervention, the median value of the total weight gain of all pads over the 24-h period was 136 g. The proportion of patients in whom incontinence was demonstrated by different tests is shown in Table 2; 24-h monitoring showed leakage in all but 4 patients (90%), 2 of whom were probably not incontinent anyway. Videourodynamics demonstrated leakage in 78% of patients. The 1-h pad test showed incontinence in fewer than half of the patients (Fig.). Even though the schedule had been simplified for geriatric use, it was followed exactly by only 22% of patients: many could not drink a sufficient volume in 15 min; others could not perform all of the activities. On visual inspection during physical examination, urine leakage was observed in only 20% of the female patients.

**Table 2** Proportion of Patients with Incontinence according to Various Methods

| | *Incontinence (%)* |
|---|---|
| History | 96 |
| 24-h monitoring | 90 |
| Video-urodynamics | 78* |
| 1-h pad test | 44 |
| Physical examination | 20† |

* 62% urge, 16% other types of incontinence.
† Females only

**Table 3** Spearman's Non-parametric Coefficients of Correlation between Amounts Leaked in 1-h Pad Tests and 24-h Monitoring Periods, before and after Intervention

| *24-h monitoring before and after intervention* | *1-h pad test before and after intervention* | *1-h pad test and 24-h monitoring before intervention* |
|---|---|---|
| 0.75<br>($P<0.001$) | 0 58<br>($P<0.001$) | 0.42<br>($P=0.001$) |

Correlations between the amounts of leakage measured before intervention and 2 to 4 weeks later are shown in Table 3. For 24-h monitoring the correlation coefficient was high, meaning that patients who leaked a large amount on the first test also leaked a large amount on the second test, and vice versa. In between the 2 tests, the patients underwent an intervention which in some cases certainly reduced but did not cure their incontinence (Table 4). The median 24-h leakage on the second occasion was 84 g (62% of that on the first). Without an intervention the correlation between the amounts leaked before and after intervention would presumably be even stronger than that in Table 3.

For the 1-h pad test the correlation between the amounts leaked in the first and second tests was weaker (Table 3). For videourodynamics a correlation coefficient is not appropriate but in 74% of patients the results of the 2 tests were identical as far as demonstration of leakage was concerned (Table 4).

The relationship between the amounts leaked during 24-h monitoring and the 1-h pad test is shown in the Figure, which also illustrates how the 1-h test failed to demonstrate leakage in a substantial proportion of incontinent patients. The correlation between the 24-h and 1-h results is weaker than that between repeated 1-h tests and much weaker than that between repeated 24-h tests (Table 3).

To enable the changes in incontinence shown by different methods to be compared, the incontinence noted after intervention was graded as "better", "worse" or "the same", relative to the pre-intervention result (Table 4). Patients were asked directly about their subjective impression of improvement or worsening, and their pre- and post-intervention replies concerning frequency of incon-

**Table 4** Post-intervention Changes in Incontinence Assessed by Various Methods

| | *Subjective history* | | | *Objective tests* | | |
|---|---|---|---|---|---|---|
| | *Impression (%)* | *Frequency of pad changes (%)* | *Frequency of incontinence events (%)* | *24-h monitoring (%)* | *1-h pad test* (%)* | *Video-urodynamics (%)* |
| Worse | 8 | 15 | 32 | 17 | 11 | 8 |
| Same | 33 | 35 | 42 | 25 | 26 | 74 |
| Better | 59 | 50 | 26 | 58 | 63 | 18 |

* Excluding patients not incontinent on either 1-h test.

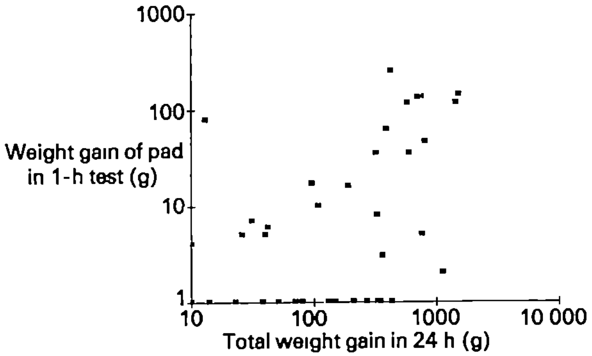

**Fig.** Weight gain of pad worn during 1-h pad test, plotted against total weight gain of all pads worn during 24-h monitoring period. Both tests were carried out before any intervention. Note that for many of the patients the plotted point lies on the horizontal axis, implying that the weight gain during the 1-h pad test was 1 g or less, so that no significant urine leakage occurred.

tinent events and frequency of pad changes were also compared. For the 24-h and pad tests "better" and "worse" implied (arbitrarily) a change of more than 25% in the total amount leaked. For videourodynamics "better" meant that leakage was demonstrated before but not after the intervention (and vice versa for "worse").

Subjectively, very few patients admitted to being worse after intervention (Table 4). Most patients with demonstrated leakage on the first videourodynamic test also leaked on the second, so that this test showed merely that there had been few (if any) cures; 24-h monitoring and the 1-h pad test both suggested that the incontinence had become less severe in more than half of the patients and worse in only a few.

Statistical (chi-squared) analysis of the results summarised in Table 4 showed no significant consistency between the various methods of judging improvement. This meant that the patients who seemed to be improved by 1 criterion (*e.g.* subjectively) were not the same as those improved by another (*e.g.* the 1-h pad test). The non-parametric coefficient of correlation between the change in the amount of leakage shown by the repeated 1-h tests and that shown by the 24-h tests was only 0.13. This low and non-significant value showed that the 2 tests did not agree on the extent to which different patients either improved or worsened.

Among patients taking oxybutinin chloride, median 24-h leakage decreased significantly from 295 g before intervention to 75 g afterwards ($P = 0.001$, Wilcoxon). Among those not taking this medication, median 24-h leakage hardly changed at all. The 1-h pad test did not show any such significant difference.

## Discussion

For objective demonstration of incontinence in this geriatric population, there is a choice between 24-h monitoring and videourodynamic testing. Both a 1-h pad test and visual inspection during physical examination frequently fail to demonstrate leakage in incontinent patients.

For grading the severity of incontinence, measurement of the total amount of leakage over a 24-h period is a satisfactory method. Differences between groups of patients can be made strikingly clear by this measurement. For example, in this study the median 24-h leakage before intervention (136 g) was 8 to 10 times greater than that in the studies of Jørgensen *et al.* (1987) (17 g) and Jakobsen *et al.* (1987b) (37 g in 48 h), showing that on average our patients were much more severely incontinent.

For assessing amelioration following an intervention, 24-h monitoring was again the most satisfactory method. Videourodynamic testing was unsuitable, even in principle. Patients' subjective reports and 1-h pad testing were too unreliable to be useful.

We suggest that 24-h monitoring should be used to confirm or exclude a diagnosis of incontinence in doubtful cases and that it should be included in research protocols designed to assess the response of incontinence to intervention. It is worth noting that, in the geriatric population, simplification by omission of the night hours is unlikely to be satisfactory, since much incontinence is nocturnal.

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# Diagnosis and Treatment of Neurogenic Bladder due to Partial Sacral Agenesis

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Summary—Fifteen patients with partial sacral agenesis were treated over a mean period of 68 months. Partial unilateral agenesis was present in 7 and bilateral sacral agenesis was present in 8. Three important diagnostic features are emphasised: symptoms referable to neurogenic bladder without an obvious neurogenic lesion (all 15 patients); skin or hair abnormalities in the lumbosacral region (9/15) and paraesthesia or other neurological disorders of the lower extremities (8/15). The definitive diagnosis can be made by careful inspection of a plain film of the lumbosacrum.

Detrusor contractility was absent in 13 patients but preserved in 2; 11 patients were managed by clean intermittent catheterisation, 2 voided using detrusor contractility and 2 voided by means of the Valsalva/Credé manoeuvre. In 5 patients surgery in the intradural space preserved sexual function and prevented further deterioration in function of the lower extremities but could not restore bladder function that had already deteriorated. Complete continence was achieved in 11 patients and socially acceptable continence in 4. Early diagnosis and conservative treatment with clean intermittent catheterisation are extremely important in management. Should functional deterioration of the bladder and/or sensomotor function of the lower limbs occur, neurosurgery should be performed promptly.

Agenesis of the sacrum is a rare congenital anomaly whose incidence ranges from 0.09 to 0.43% (Koontz and Prout, 1968; White and Klauber, 1976). Approximately 200 cases have been reported in the literature (Mariani *et al.*, 1979). In these patients, involvement of the second to fourth sacral nerve roots usually compromises both lower urinary tract and sexual function. This disorder is frequently associated with myelomeningocele or the tethered cord syndrome (Pang and Hoffman, 1980; Hafeez and Tihansky, 1984). We present our experience in diagnosing and managing 15 patients with partial sacral agenesis.

## Patients and Methods

Between 1977 and 1989 we treated 15 patients with partial sacral agenesis (7 males and 8 females aged 1–27 years; mean 10.9 years). Excluded were patients with meningomyelocele. Characteristics of the 15 patients are shown in Table 1. When first seen, 8 patients voided by using the Valsalva/Credé manoeuvre, 3 by overflow urine, 1 by clean intermittent catheterisation and 1 had an indwelling catheter. Only 2 voided by using detrusor contractility. The mother of 1 patient had insulin-dependent diabetes.

The sacral anomaly was confirmed by plain X-

**Table 1** Characteristics of 15 Patients

| | |
|---|---|
| Ratio of males to females: 7:8 | |
| Age range: 1 to 27 years (mean 10.9) | |
| Urological signs and symptoms | |
| Incontinence | 9 |
| Difficulty in urination | 9 |
| Frequency | 5 |
| Urinary tract infection | 4 |
| Weak stream | 1 |
| Length of follow-up: 68 months (range 8–119) | |

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ray. The classification of Borrelli *et al.* (1985) was used to categorise the bony defect. Urodynamic studies were performed in all cases a few weeks after the initial visit and were repeated in 10 patients an average of 47 months after the start of treatment. Cystometry was performed by infusing 30% contrast medium through an 8 or 10F double lumen catheter passed into the urethra (30–40 ml/min). Detrusor pressure was calculated by subtracting the abdominal pressure from the bladder pressure, thus enabling bladder compliance ($\Delta V/\Delta P$) and involuntary detrusor contractions (> 15 cm of water) to be assessed. Intermittent fluoroscopic monitoring of the lower urinary tract was done to evaluate reflux and the severity of bladder trabeculation. Methods, definitions and units conform to the standards proposed by the International Continence Society except where specifically noted.

### *Vertebral, dermal and neurological findings*

On X-ray the sacral deformity was consistent with type I in 7 patients, partial unilateral sacral agenesis, and type II in 8, partial bilateral sacral agenesis (Fig. 1). Abnormalities of the skin or hair in the lumbosacral region were observed in 5 patients and included pigmentation, scarring or abnormal hair pattern (Fig. 2). Another 4 had a small scar in that area, indicating previous surgical removal of a small cutaneous abnormality. Eight patients had motor and/or sensory disorders of the lower extremities and 11 had decreased anal tonus.

### *Lower urinary tract function*

The type of bladder dysfunction in these patients was characterised urodynamically by motor paralysis of the bladder, observed in 13 cases (Table 2); involuntary detrusor contractions were present in 10. Of the 10 patients who were reassessed 47 months after the start of treatment, including 2 with stable bladders, involuntary contractions disappeared or were downgraded in 7 of the 8 patients with detrusor areflexia (Fig. 3). Bladder compliance increased significantly.

### *Upper urinary tract function*

Vesicoureteric reflux was observed in 5 ureters (3 patients). High grade reflux (> grade III) was found in 3 ureters. A moderate deterioration in renal function was found in 1 patient (creatinine clearance 67 l/day) and 3 patients with reflux had hydronephrosis.

## Results

As a result of their urodynamic assessment, 11 patients began clean intermittent catheterisation, 2 continued to void by abdominal straining and 2 voided using detrusor contractility. At present 3 patients receive anticholinergic drugs to augment their bladder capacity and to prevent urinary incontinence. One of the 3 patients with reflux received a teflon paste injection at the periureteric

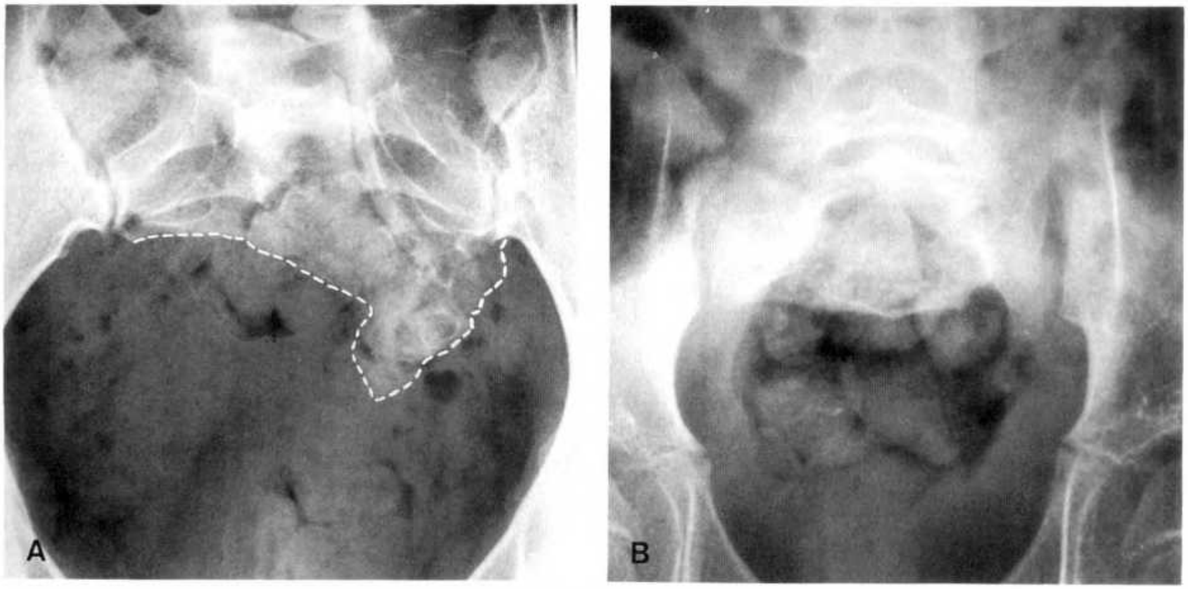

**Fig. 1** Anteroposterior view of the lumbosacrum showing (A) unilateral (right) sacral agenesis and (B) bilateral sacral agenesis.

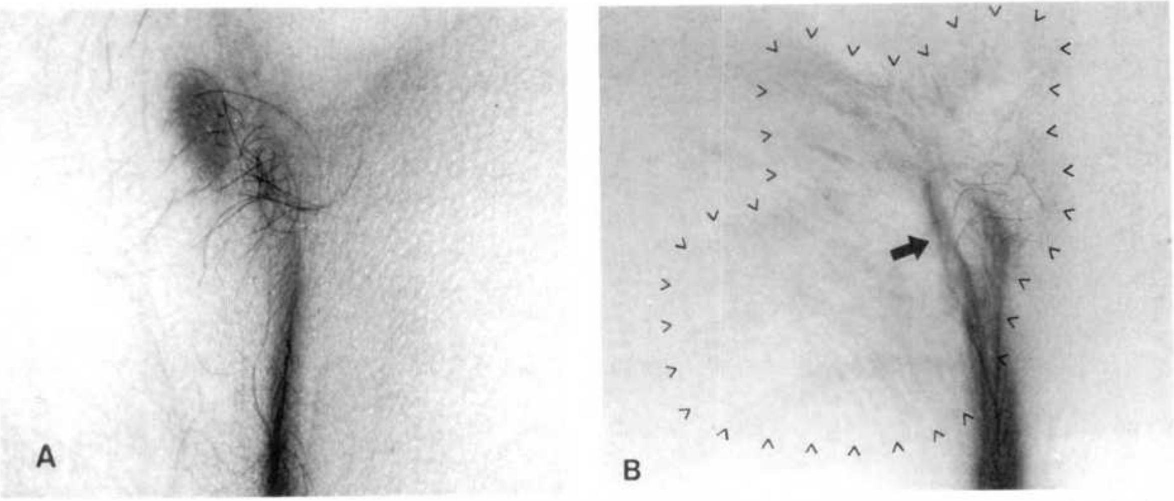

Fig. 2 Skin abnormalities in the lumbosacral area. (A) Pigmentation and abnormal hair pattern. (B) Congenital skin scarring (surrounded by Vs) and lateral deviation of crena ani (arrow).

orifice (Puri and Guiney, 1986) without success. Another patient had undergone antireflux surgery 8 years earlier at another hospital. Nine patients who were referred to a neurosurgeon were found to have the tethered cord syndrome, caused either by filum terminale or by an intradural lipoma. Three of these patients subsequently underwent surgery to "untether" the cord and 2 had previously undergone that operation before attending our clinic. Surgery was intended to prevent progression of the paraesthesia and other symptoms in the lower extremities, and to preserve sexual function, but it could not restore bladder function that had already declined. With treatment, socially acceptable continence was attained by 4 of the 15 patients and the remaining 11 were completely continent.

**Table 2** Results of Urodynamic Investigation

| | |
|---|---|
| Initial study (n = 15) | |
| Detrusor areflexia | 13 |
| Stable bladder | 2 |
| Bladder compliance | 10.5 ml/cm $H_2O$ (1.4–37) |
| Involuntary contractions | 10 |
| Second study (n = 10) | |
| Detrusor areflexia | 8 |
| Stable bladder | 2 |
| Bladder compliance | 15.1 ml/cm $H_2O$ (2.5–37.5) |
| Involuntary contractions disappeared or downgraded in 7/8 patients; other 2 patients had stable bladders | |

## Discussion

While high grade sacral agenesis is easy to diagnose at birth, partial sacral agenesis presents a diagnostic challenge. A firm diagnosis can be made only when the patient complains of a disorder of bladder function and/or of the lower extremities. Symptoms appeared in 3 of our patients when aged less than 5 years, at the of 7–15 years in 9 and over 20 years of age in 3.

Three important clues can lead to the correct diagnosis of partial sacral agenesis. First, the development of urological symptoms as listed in Table 1; bladder disorders without an obvious neurogenic lesion imply sacral involvement. Second, skin abnormalities in the lumbosacral area may suggest a congenital abnormality of the vertebrae (present in 9 of our patients, 4 of whom had undergone cosmetic surgery without evaluating the true pathology of the intradural space). Third, disorders of the lower extremities, ranging from sensory disturbance (pain or numbness) to muscular atrophy, indicate damage to the lumbosacral nerves. These symptoms were found in 8 patients. Four patients had all 3 of the above factors, 9 had 2 and 2 had only the urological disorders.

If unexplained bladder dysfunction is found, with or without urinary infection, the so-called occult neurogenic bladder should be suspected. The next step is to arrange a plain X-ray of the lumbosacrum. Careful inspection and investigation of the lumbosacral area and of the lower extremities will lead to a diagnosis of partial sacral agenesis. The diagnosis can be confirmed by inspecting a plain film. It is important to remember that any abnormalities of the sacrum are closely related to the cause of bladder dysfunction. In addition, the family history may be informative, *e.g.* maternal

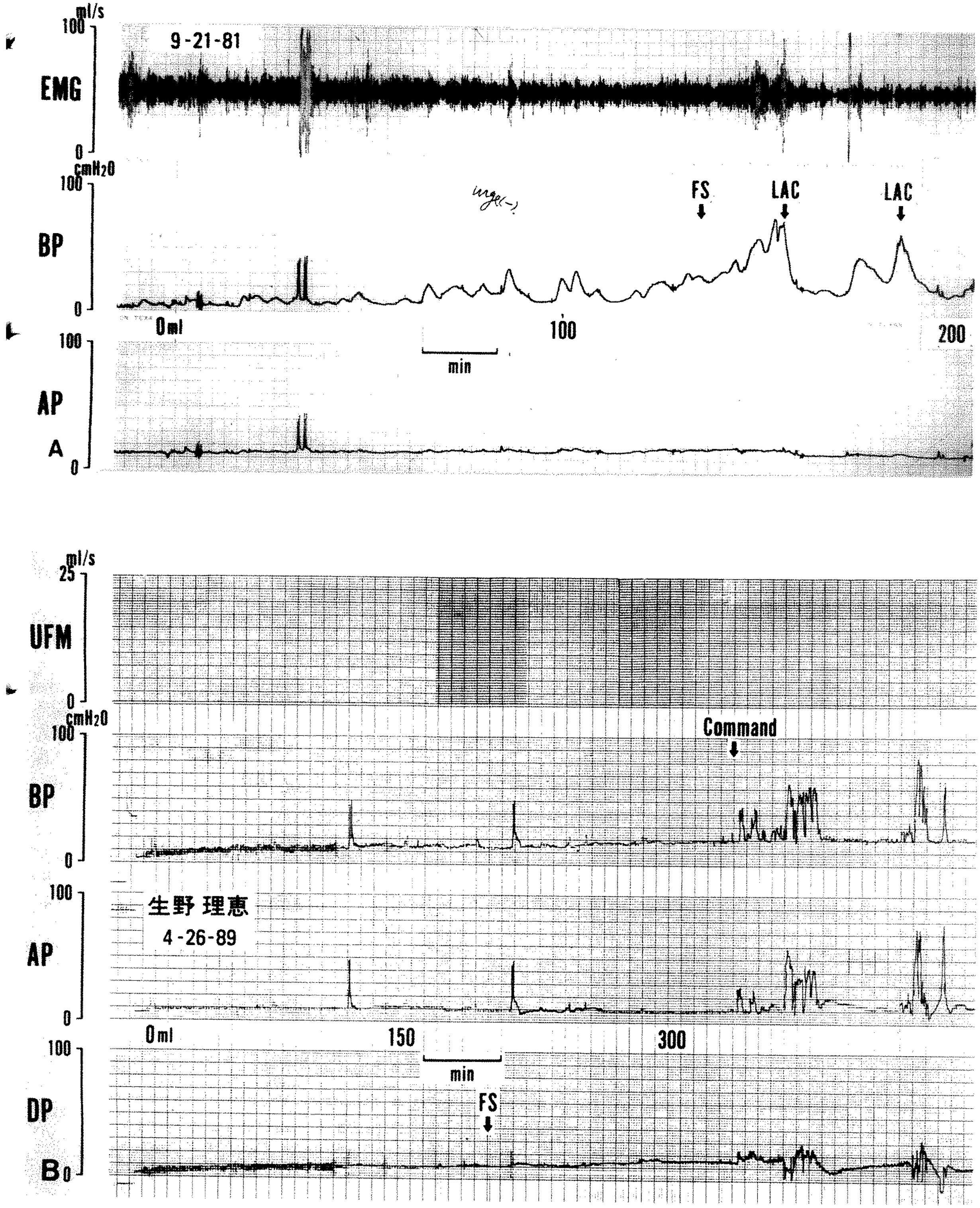

**Fig. 3** Urodynamic study in an 8-year-old girl with partial sacral agenesis. (A) Initial study. (B) Eight years later. EMG: electromyography of external urinary sphincter. UFM: uroflowmetry. BP: bladder pressure. AP: abdominal pressure. DP: detrusor pressure. LAC: leakage around catheter. FS: first sensation. Command: command to void.

diabetes mellitus is occasionally associated with sacral agenesis (Andrish *et al.*, 1979; Braren and Jones, 1979). However, in our series this history was found in only 1 case.

Urodynamic studies will reveal varying degrees of bladder paralysis, with involuntary contractions present in most of the untreated patients. Williams and Nixon (1957) stated that the type of bladder disturbance seemed unrelated to the type of bony deformity. Koff and Deridder (1977), who examined 11 patients by means of cystometry, found that 3 had an upper motor neuron lesion, 4 a lower motor neuron lesion and 4 had a mixed type. We found that detrusor contractility was absent in 13 of our patients, despite the presence of involuntary contractions, and was preserved fairly well in only 2. The most useful form of treatment is clean intermittent catheterisation, which decreases or abolishes the involuntary contractions. Eleven patients now carry out clean intermittent catheterisation, 2 void by using detrusor contractility and 2 by the Valsalva/Credé manoeuvre. Urological surgery is usually unnecessary, apart from the antireflux procedures which were required in 2 of our patients.

The indications for surgery on the intradural space in these patients remains controversial. Although some authors believe that the tethered cord with sacral agenesis should be resected in all cases (Pang and Hoffman, 1980; Hafeez and Tihansky, 1984), one has to weigh the advantages and disadvantages of such surgery in the individual. In the present series, neurosurgery was undertaken in 5 patients with a diagnosis of intradural lipoma or tight filum terminale, where sacral roots travelled in a cephalad direction. Of these 5 patients, 2 had been operated on prior to attending our clinic and we referred 3 patients for surgery. The outcome was disappointing as far as restoration of bladder function was concerned, confirming our previous observations on the untethering operation (Kondo *et al.*, 1986). In that study of patients with sensomotor paralysis of the bladder, symptoms had been present for more than 3 years and skin abnormalities did not improve. However, we believe that the operation was helpful in preserving sexual function in 3 young men, an important clinical consideration, and also in preventing further deterioration in the function of the lower extremities. Of the 5 patients who underwent surgery, none felt that their symptoms were aggravated by the operation. Surgery should be considered in a patient with progressive bladder dysfunction and/or progressive sensomotor disorder of the lower limbs.

## Acknowledgement

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# Abnormalities of Colonic Mucin Secretion and Metabolic Changes after Internal Urinary Diversion for Bladder Exstrophy

## A Prospective Study

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Summary—Ten patients with different types of internal urinary diversion for bladder exstrophy were studied prospectively in order to assess metabolic abnormalities and morphological, histochemical and lectin binding changes in the colorectal mucosa. The histochemical and/or lectin binding changes which were found in the majority of patients were identical to those observed in pre-malignant and malignant conditions of the colon. In some cases they were detectable 3 years after the initial examination but were completely absent from the colorectal mucosa of normal subjects. Metabolic disturbances (metabolic acidosis, increased anion gap, hyperchloraemia) were observed in a substantial number of asymptomatic patients. These findings stress the need for regular endoscopic, histological and metabolic follow-up in these patients and for life-long treatment with bicarbonate or citrate.

Internal urinary diversion (IUD) is associated with an increased risk of colonic carcinoma. This risk has been assessed with particular reference to ureterosigmoidostomy (Crissey *et al.*, 1980; Stewart *et al.*, 1982; Schwab *et al.*, 1986), but there is growing evidence that other types of IUD (colon conduit, ileal conduit) should also be regarded as pre-neoplastic conditions (Moorcraft *et al.*, 1983; Marchetti *et al.*, 1984; Stone and Stephenson, 1987; Strand and Alfert, 1987). Since IUD is frequently performed in infants and young children as part of a reconstructive procedure of the genitourinary tract, it is important to identify a marker of colonic pre-malignancy. This would allow early recognition of patients who will eventually develop a tumour. No reliable methods have yet been reported, but qualitative studies (using histochemical or lectin binding methods) of colonic mucus, which represents the metabolic end product of goblet cells, could reveal subtle alterations in the metabolic pathway of these cells. Changes in normal mucus are found in neoplastic and pre-neoplastic conditions (Boland *et al.*, 1982a and b, 1984) and are considered to be the morphological result of the metabolic disturbance. By analogy, their presence may identify subclasses of patients at increased risk of developing cancer.

In previous studies (Marcheggiano *et al.*, 1984; Iannoni *et al.*, 1986), we demonstrated histochemical and lectin binding changes, similar to those found in pre-neoplastic conditions, in the rectosigmoid mucosa of adult patients with a ureterosigmoidostomy (USS) or rectal bladder (RB) performed for malignant bladder conditions. In the present prospective study, using histochemical and lectin binding methods, we have examined the rectosigmoid mucosa of young USS and RB patients operated on for bladder exstrophy, in order to assess whether they too had changes similar to those observed in adults; we also studied the possible evolution of these changes.

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Since it is well known that USS and RB have systemic metabolic consequences, acid-base balance and serum electrolytes were studied. Electrolyte composition and the pH of urine from RB patients and the urine-faeces mixture from USS patients were also evaluated.

## Patients and Methods

Ten patients (8 males and 2 females) were enrolled in a surveillance programme involving 2 endoscopic and histological examinations, spaced 3 years apart, together with electrolyte and acid-base evaluations. Eight patients had rectal bladders and 2 had ureterosigmoidostomies. Their mean age at operation was 5.9 years (range 4–10); the mean duration of IUD at the first assessment was 12.1 years (range 1–21). The first flexible colonoscopy or sigmoidoscopy was performed in 1986 and the second 3 years later. At least 2 biopsies (range 2–6) were taken from the ureteric orifices, 5 cm apart, in each patient. In all, 28 biopsies were taken during the first endoscopy and 62 during the second.

Twenty biopsy specimens taken from uninvolved transitional mucosa (TM) adjacent to colorectal carcinomas in 10 patients (mean age 39 years, range 28–45; 7 males and 3 females) were also included in the study.

Twenty normal rectal biopsy specimens from 10 patients (mean age 20 years, range 15–25; 8 males and 2 females), who were undergoing sigmoidoscopy for haemorrhoids, were used as controls.

## Staining Methods

All specimens were oriented, fixed in Bouin's fluid and processed routinely. Serial sections prepared from each paraffin block were stained with haematoxylin and eosin for routine histological examination.

For the histochemical studies, slides containing at least 30 serial sections (5 µm thick) were investigated by the high iron diamine-alcian blue method (HID-AB) at a pH of 2.5 (Spicer, 1965). The slides were observed by one of us who was unaware of the clinical data. The semiquantitative evaluation was performed as described previously (Marcheggiano *et al.*, 1984; Iannoni *et al.*, 1986), by assessing the proportion of HID+ and AB+ cells in the entire biopsy specimen in at least 2 sections 30 µm apart and assigning separate scores for HID+ and AB+ cells according to the following scheme: 0, no positive cells; 1, one-third of cells positive; 2, one-half of cells positive; 3, two-thirds of cells positive; 4, all cells positive.

Two fluorescein-conjugated (FITC) lectins (Sigma Chemical Company, St Louis, USA) were used to study the lectin binding pattern of epithelial mucosubstances: Dolichus biflorus agglutinin (DBA), which binds to complete glycoproteins of normal colorectal mucosa, and Arachis hypogaea agglutinin (PNA), which does not bind to glycoproteins of normal mucosa, while labelling glycoproteins of neoplastic and pre-neoplastic mucosa. Tissue sections were incubated with the FITC-lectins as described previously (Iannoni *et al.*, 1986). The pattern of fluorescence was examined immediately and photographed with a Leitz Orthoplan microscope equipped for epifluorescence. Labelling intensity was graded 0–4 according to the proportion of fluorescent crypts, in 2 sections 30 µm apart, and the counts were averaged. Student's *t* test was used for statistical analysis.

## Serum Electrolytes, Acid-base Balance, Analysis of Urine and Urine-faeces Mixture

All patients underwent intravenous urography during the 2 months prior to the present investigation. At the time of the first endoscopic examination, venous blood samples were collected for the determination of nitrogen, creatinine, sodium, potassium and chloride levels. Arterial blood samples were collected for the determination of acid-base balance (blood gas analyser radiometer). The anion gap was calculated using the following formula: $(Na^+)-((Cl^-)+(HCO_3^-))$. On the day of blood sampling, urine and urine-faeces mixture specimens were collected for the determination of pH, sodium, potassium, chloride and bicarbonate, using a previously reported method (Caprilli *et al.*, 1986a). None of the patients was on a chloride-restricted diet or receiving bicarbonate supplement or medication which might interfere with electrolyte metabolism.

## Results

*Histological findings (IUD group).* Mild chronic inflammation and changes in the mucosal architecture with crypt distortion were observed in the majority of biopsy specimens from both the first and the second examinations (Fig. 1). The number and morphology of goblet cells appeared normal.

*Histochemical studies of mucin.* By using the HID-AB pH 2.5 method a virtually absolute prevalence of AB+, sialomucin-containing goblet cells was observed in both IUD patients and TM patients when compared with normal subjects (Table 1). Only a few residual cells contained HID+ sulphomucins. In IUD patients this pattern of mucin secretion was unchanged after 3 years.

**Table 1** Scores (mean ± SD) for HID+ and AB+ Colonic Epithelial Cells

| *Group* | *HID* | *AB* |
|---|---|---|
| Controls | 2.8±0.4 | 1.7±0.3 |
| Internal urinary diversion | 0.3±0.5 | 3.7±0.5 |
| Transitional mucosa | 1.1±0.9 | 3.3±0.5 |

Control group versus internal urinary diversion and transitional mucosa groups $P<0.001$.
HID: high iron diamine, AB: alcian blue.

*FITC-lectin binding Studies.* FITC-DBA strongly labelled goblet cell mucin of rectal and sigmoid mucosa from the control group. In the TM and IUD groups, the mucosa showed a dramatic decrease in labelling and in many cases binding was virtually absent. The second series of biopsies from the IUD group gave identical results. FITC-PNA binding was completely absent from rectal and sigmoid mucosa specimens taken from control subjects. At least 1 specimen from each patient in the TM group showed FITC-PNA binding in the mucin secreted into the crypts and the goblet cells. PNA positivity (Fig. 2) was found in 11 of 15 biopsy specimens taken during the initial endoscopy in 6 IUD patients, while the other 4 patients (13 biopsies) were PNA negative. In the second examination, PNA positivity was found in 19 of 21 biopsies from 3 patients who were PNA+ in the first examination; 1 patient who was PNA− in the first examination became PNA+; 3 patients who were PNA+ became PNA−, and 3 patients remained PNA−. Taking the first and second examinations together, 7 of 10 patients showed PNA positivity at some point and only 3 were consistently PNA negative. The mean duration of IUD in these 3 patients was similar to that of the other 7 (12 and 11.4 years respectively). The results of the lectin binding evaluation are summarised in Table 2.

*Serum Electrolytes, Acid-base Balance, Analysis of Urine and Urine-faeces Mixture.* Metabolic acidosis (pH 7.32±0.03; $HCO_3^-$ 17.9±1.3; B.E. −6.8±2.2) was present in 60% of patients (5 RB and 1 USS). Acidosis was associated with an increase in the anion gap in 30% of patients. In these patients the mean value of the anion gap was 20.6±1.5. Plasma levels of sodium and potassium were unchanged in all patients, whereas hyperchloraemia (114±2.6 mEq/L) was present in 40%. All patients showed normal values of azotaemia and creatininaemia.

**Table 2** Scores (mean ± SD) for FITC-DBA Positive and FITC-PNA Positive Colonic Epithelial Cells

| *Group* | *FITC-DBA* | | *FITC-PNA* | |
|---|---|---|---|---|
| | 1st* | 2nd† | 1st* | 2nd† |
| Controls | 4.0±0 | 4.0±0 | 0±0 | 0±0 |
| Internal urinary diversion | 0±0 | 0±0 | 0.7±1 | 0.5±1.1 |
| Transitional mucosa | 0.6±0.4 | 0.6±0.4 | 1.6±0.8 | 1.6±0.8 |

*First examination, †After 3 years
Control group versus internal urinary diversion and transitional mucosa groups $P<0.001$.
FITC-DBA: fluorescein-conjugated Dolichus biflorus agglutinin, FITC-PNA: fluorescein-conjugated Arachis hypogaea (peanut) agglutinin.

Intravenous urography was normal in 7 patients; 1 had pyelonephritis and a renal stone and 2 had mild hydronephrosis.

The mean daily output of urine in RB patients and the urine-faeces mixture in USS patients was 1375 and 2250 ml respectively. $HCO_3^-$ and pH were significantly lower in urine than in the urine-faeces mixture (8.7±2.8 *vs* 15.6±5.1 mEq/L, 6.2±0.3 *vs* 7.7±0.1, $P<0.001$). The daily excretion of $Na^+$, $Cl^-$ and $K^+$ was 91.5±21.3, 108.1±39.5 and 43.6±16 mEq/L in RB patients and 104±26.8, 134±48.7 and 24.5±12 in USS patients.

## Discussion

The high risk of cancer that accompanies USS is well known. However, many reports suggest that various types of IUD are also associated with an increased risk (Marchetti *et al.*, 1984; Stone and Stephenson, 1987; Strand and Alfert, 1987). It may be that this trend is becoming clearer as the duration of IUD increases. A cause and effect relationship undoubtedly exists between IUD and the subsequent development of neoplasm of the colon and evidence suggests that the main site for neoplastic transformation is the ureterocolic junction. Many theories have been put forward to explain this phenomenon but none seems satisfactory. It is unlikely to be attributable to a single factor but may represent the sum of several factors, the relative importance of each being difficult to assess. Factors claimed to be significant in the induction of neoplasia are altered bowel mechanisms, the irritative effect of urine, a high concentration of electrolytes, glandular metaplasia of the ureteric stump (Chiarelli and Sandei, 1984), the production of N-nitrosoamines (Stewart *et al.*, 1982) and chronic inflammation and atrophy of colonic mucosa adjacent to the ureteric implant sites (Mostofi *et al.*, 1955). The last point is particularly controversial. In previous studies (Gilchrist *et al.*, 1984; Marcheggiano *et al.*, 1984; Iannoni *et al.*, 1986), no evidence of inflammation was found, either in biopsies from the ureteric site or in those taken some distance away from it. However, mild chronic inflammation was demonstrated in the rectosigmoid mucosa of almost all patients in both the first and second biopsy series. This discrepancy is hard to explain, but it is possible that the long duration of IUD in these patients could have played a part. However, the fact that inflammation was not a consistent finding and that it was present some distance away from the ureteric site suggests that it is not a primary risk factor.

This study confirms previous observations concerning changes in the mucus in IUD patients (Marcheggiano *et al.*, 1984; Iannoni *et al.*, 1986; Tomasino *et al.*, 1987). In fact, the histochemical and lectin binding pattern of colonic mucosubstances was abnormal in both the first and second biopsy series.

Using the HID-AB pH 2.5 method, histochemical changes identical to those already described (Marcheggiano *et al.*, 1984; Iannoni *et al.*, 1986) were unchanged after 3 years; their distribution was diffuse and not confined to the ureteric site, where neoplasia develops. Moreover, as has been previously demonstrated (Iannoni *et al.*, 1986), in USS the alterations developed early, while in RB of short duration a normal histochemical pattern was found. These considerations may indicate that it is a non-specific phenomenon, probably secondary to environmental factors (Isaacson and Attwood, 1979; Lev *et al.*, 1985).

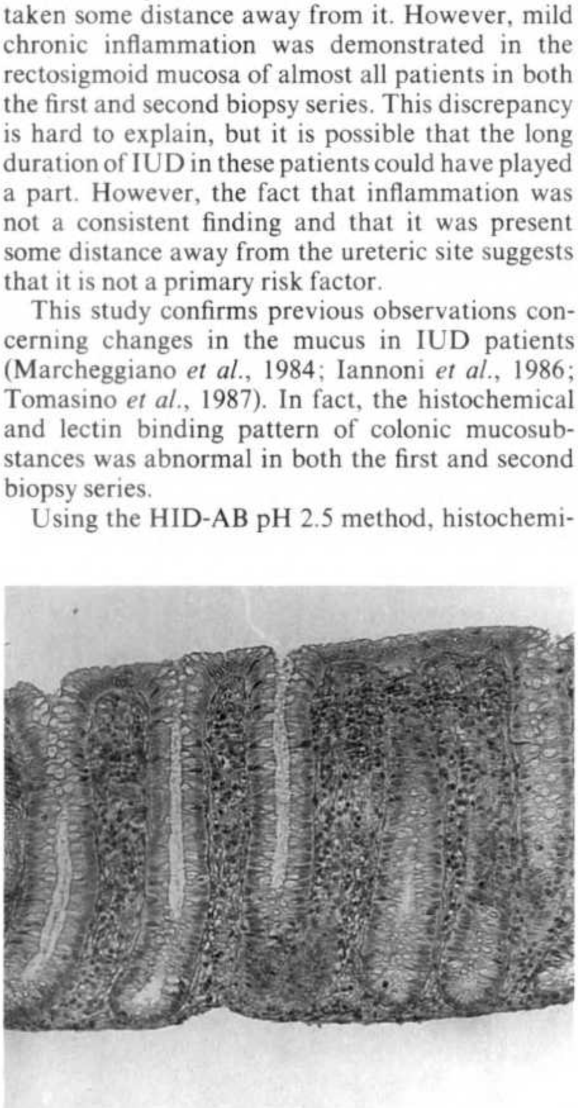

**Fig. 1** Biopsy specimen taken near the site of implantation of the ureters in a patient with rectal bladder. A mild chronic inflammatory infiltrate is seen in the "lamina propria" of this otherwise normal rectal mucosa. (H and E × 100).

Studies with FITC-lectins revealed an abnormal lectin binding pattern in the colorectal mucosa of IUD patients in both biopsy series. This abnormality was identical to that observed in colonic cancer, adenomatous polyps, TM and long-standing ulcerative colitis (Boland *et al.*, 1982a and b, 1984) and in IUD patients undergoing surgery for carcinoma of the bladder (Iannoni *et al.*, 1986). It consists of a marked decrease in the numbers of DBA+ cells and the appearance of variable amounts of PNA+ cells. Although it has been considered to be an expression of cell immaturity, DBA disappearance has not been directly associated with neoplasia, while the appearance of PNA+ cells has been related to the local production of a cancer-associated mucosubstance (Boland *et al.*, 1982a and b). However, as in HID-AB, the major arguments against any supposed link between changes in the mucus demonstrable by lectins and the risk of neoplasia in these patients are the diffuse nature of the phenomenon, which is not confined to the ureteric site where neoplasia usually develops, as well as the early development of mucus changes when compared with the long time interval which is needed for neoplasia to develop. It may be that alterations in the mucus, which reflect the metabolic derangement of goblet cells, become relevant only in the presence of factors produced locally at the ureteric sites, perhaps by the ureteric mucosa, which may behave synergically. This view is supported by the observation that after diversion of urine ("dry IUD"), the site of implantation of the ureters may undergo malignant transformation (Schipper and Decter, 1981), thus suggesting that the role of luminal factors is not essential.

An interesting finding is the observation that PNA positivity is a dynamic and potentially reversible phenomenon. Of 6 patients who showed PNA positivity in their rectal mucosa at the initial biopsy, the 3 patients with strong positivity (2+/3+) remained positive, while the others, who showed only slight positivity (1+), became negative

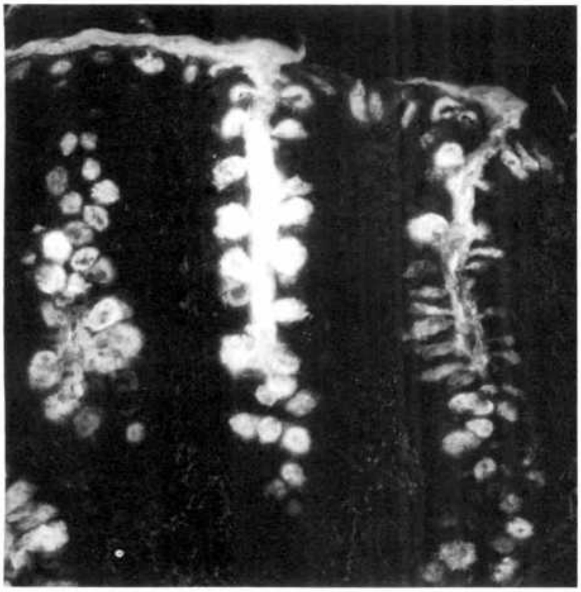

**Fig. 2** FITC-PNA labelling. Rectal biopsy specimen from a patient who underwent rectal bladder surgery showing brightly fluorescent PNA-labelled goblet cells in the superficial and crypt epithelium. (× 250).

after 3 years. Patients with strong positivity showed the same pattern in all biopsy specimens, while a more patchy distribution of PNA + cells was found in patients with slight positivity. We suggest that strong PNA positivity may identify a subclass of patients in whom the mucus alteration is well established and diffuse and does not revert to normal. Time will tell whether these patients are at risk of developing cancer.

Of immediate clinical relevance is the observation that metabolic disturbances are present in these patients. Metabolic acidosis was observed in 60%, while an increase in the anion gap was present in only 30%. Hyperchloraemia was found in 4 of 10 patients, while plasma levels of sodium and potassium were normal.

The pathogenesis of metabolic acidosis is not yet completely clear. One of the proposed mechanisms is considered to be the increased intestinal loss of bicarbonate (McConnel *et al.*, 1979).

In normal subjects, the overall daily loss of bicarbonate in the faeces and urine is about 6 mEq (Caprilli *et al.*, 1986a and b); in the present series it was about 35 mEq and 16.5 mEq (12 in urine and 4.5 in faeces) respectively in patients with USS and RB. These findings may also explain why, in patients with RB, the metabolic change was less severe than in those with USS and often clinically silent. Metabolic acidosis in USS is generally held to be of the hyperchloraemic type and to have a normal anion gap (Kaehni and Gabon, 1980). In the present series, hyperchloraemia was present in only 40% of patients and the anion gap was increased in 30%. Hyperchloraemia may be due to enhanced colonic reabsorption of chloride, which is related in part to anionic exchange with the secretion of bicarbonate, and in part to active sodium absorption (Davis *et al.*, 1983).

The enhanced anionic $Cl/HCO_3$ exchange may explain the metabolic acidosis but does not explain the hyperchloraemia and especially why this is present only in some patients. If the pathogenesis of hyperchloraemia results from this mechanism, hyperchloraemia and the base deficit should always be associated. This was not the case in the present series. On the other hand, it is known that only 25% of intestinal absorption of chloride occurs through $Cl/HCO_3$ exchange, with the remainder diffusing passively via intercellular pathways down the electrochemical gradient generated by electrogenetic Na absorption (Davis *et al.*, 1983). Despite the continuous reabsorption of chloride, chloraemia was normal in most of our IUD patients, thus indicating that the enhanced intestinal absorption of chloride was balanced by the increased renal excretion of this ion. It is possible that hyperchloraemia, when present, is produced on the basis of the law of electroneutrality in order to balance the reduction in plasma bicarbonate. When chloraemia was normal, the balance was maintained through the increase of the anion gap (Oh and Carroll, 1977). The increased anion gap found in IUD may result from the increase in unmeasured anions, *i.e.* inorganic acids such as phosphates and sulphates, probably due to defective renal excretion of these ions (Caprilli *et al.*, 1986a and b). In the present series of IUD patients the increase in the anion gap was encountered less frequently, compared with what was previously found in adult IUD patients (Caprilli *et al.*, 1986a and b). This may be due to the better renal function shown by these young patients.

This study confirms the high incidence of metabolic acidosis in RB, demonstrating that even a short tract of colonic mucosa bathed in urine is sufficient to produce systemic electrolyte and metabolic alterations and that the mixture of faeces and urine does not represent a determining factor in the onset of such modifications (Caprilli *et al.*, 1986a and b). Since systemic metabolic changes are also present in asymptomatic patients, it is obvious that IUD patients require careful surveillance. Periodic assessment of electrolytes, acid-base balance and anion gap, and continuous treatment with oral bicarbonate or citrate are necessary.

The present study has confirmed the persistence of changes in the rectal mucosa of young patients with IUD, similar to those found in cancer and preneoplastic conditions. Longer follow-up is necessary to determine the specificity of these findings and prospective, long-term studies should be performed in IUD patients. However, we feel that evaluation of goblet cell mucin by lectins is a promising approach in assessing the neoplastic risk in IUD.

The demonstration of metabolic abnormalities in asymptomatic patients suggests the need for regular follow-up and for life-long treatment with bicarbonate or citrate.

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# Bladder Instillations of Trisdine Compared with Catheter Introducer for Reduction of Bacteriuria during Intermittent Catheterisation of Patients with Acute Spinal Cord Trauma

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Summary—An open, prospective, randomised trial was conducted to compare the incidence of significant bacteriuria following 2 methods of intermittent urethral catheterisation in patients with acute spinal cord trauma. Twenty-two patients were catheterised with a Nelaton catheter and 50 ml of Trisdine were instilled into the bladder and left there immediately prior to withdrawal of the catheter. Fifteen patients were catheterised with a Nelaton catheter with a special introducer to improve asepsis (O'Neil catheter). The mean incidence of significant bacteriuria in males and females who received Trisdine bladder instillations was 0.58 and 0.48% per catheterisation respectively; in males and females catheterised with the O'Neil catheter it was 1.16 and 2.93% per catheterisation respectively. The instillation of Trisdine into the bladder after each passage of a catheter resulted in a significantly lower incidence of bacteriuria compared with that which resulted from the use of the O'Neil catheter. The former method is therefore to be preferred for aseptic intermittent urethral catheterisation in patients with acute spinal cord trauma.

Aseptic intermittent urethral catheterisation is often used for the initial bladder management of patients with acute spinal cord trauma. The occurrence of significant bacteriuria in these patients frequently leads to symptomatic urinary tract infection with fever. Therefore, spinal units which employ aseptic intermittent catheterisation for initial bladder management try to keep the incidence of catheter-induced bacteriuria to a minimum.

Attempts have been made to eliminate organisms in the lower urethra by injecting a lubricant containing a disinfectant, such as chlorhexidine gluconate 0.5%, into the urethra before passing a catheter, but this was not found to be very effective in reducing the incidence of catheter-induced bladder infections (Gillespie *et al.*, 1962). Several studies over the last 30 years, however, have demonstrated that disinfection of the bladder immediately after it has been contaminated with urethral organisms carried in by the catheter is highly effective in reducing the incidence of bacteriuria associated with intermittent catheterisation (Paterson *et al.*, 1960; Gillespie *et al.*, 1962; McFadyen and Simmons, 1968; Pearman, 1979). This has been achieved by instilling 25 to 60 ml of various antimicrobial solutions into the bladder at the end of each catheterisation. Trisdine has been shown to be an effective and safe disinfectant solution for this purpose (Pearman *et al.*, 1988). Trisdine is an aqueous solution of chlorhexidine gluconate 0.01% with added ethylenediaminetetraacetic acid disodium salt and TRIS buffer at final concentrations of 1.34 mMoles and 0.01 Molar respectively. Unlike higher concentrations of chlorhexidine, frequent and repeated instillations of Trisdine into the bladder do not cause chemical cystitis or haematuria (Pearman *et al.*, 1988).

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A new technique of catheterisation has been developed by O'Neil (1981), who showed that the lower urethra of 90% of the female patients in his study harboured bacteria. However, when a swab introduced into the urethra was protected by a sheath to a depth of 1.5 cm, bacteria were cultured from only 10% of these patients. The O'Neil catheter has a similar introducer sheath (1.5 cm long) which is designed to reduce contamination of the catheter by organisms normally resident in the distal 1.5 cm of the urethra (O'Neil *et al.*, 1982).

In a clinical trial, 17 of 67 females (25%) had bacteriuria after intermittent catheterisation with a Nelaton catheter, whereas only 2 of 52 females (3.85%) intermittently catheterised with the O'Neil catheter developed post-catheterisation bacteriuria (O'Neil *et al.*, 1982).

We report the results of an open, prospective, randomised trial which compared the incidence of significant bacteriuria associated with the use of 2 different methods of intermittent urethral catheterisation in patients with acute spinal cord trauma: (1) a Nelaton catheter with instillation of 50 ml of Trisdine into the bladder at the end of each catheterisation, and (2) a Nelaton catheter with a special introducer to improve asepsis during passage through the lower end of the urethra (the O'Neil catheter).

## Patients and Methods

All patients admitted to the Perth Spinal Department between 1 March 1988 and 31 August 1989 with acute spinal cord trauma and bladder involvement requiring intermittent catheterisation for more than 5 days were asked to participate in the trial. Patients with minimal bladder involvement, who were intermittently catheterised for only 5 days or less, were excluded. Patients were randomly assigned to 1 of 2 groups according to the last digit of their unit medical record number; patients with even numbers were placed in group A and those with odd numbers in group B.

A total of 43 patients (36 males, 7 females) were admitted with acute spinal cord trauma and were intermittently catheterised for more than 5 days. Random assignment resulted in 19 males and 1 female being placed in group A and 17 males and 6 females in group B. Six males assigned to group B did not have the O'Neil catheter; 4 did not give permission, 1 withdrew after the O'Neil catheter had been used for 24 days because its passage caused urethral pain, and another with a history of urethral stricture following pelvic trauma did not have the O'Neil catheter on the advice of a consultant urologist. Two females assigned to group B also refused permission for the O'Neil catheter to be used. The remaining 11 males and 4 females who were catheterised by the O'Neil technique constituted group B.

Randomisation resulted in only 1 female patient being assigned to group A. Therefore the 2 females randomised to group B who did not give permission for the O'Neil catheter to be used (and who were managed by Nelaton catheterisation with Trisdine bladder instillation) were added to group A, making a total of 3 females in this group.

In group A the mean age of the males was 29 years (range 17–52) and the mean age of the females was 46 years (range 22–70). In group B the mean age of the males was 22 years (range 13–41) and that of the females was 33 years (range 20–45). There was no significant difference in the mean age of patients in each group.

### Bladder management

*Group A. Intermittent catheterisation by a Nelaton catheter with the instillation of Trisdine into the bladder at the end of each catheterisation.* A sterile, disposable, polyvinyl chloride Nelaton catheter, size 14 F (manufactured by Travenol or Indoplas), was used and each catheterisation was carried out according to the standard non-touch techniques of intermittent catheterisation used in the Perth Spinal Department (Pearman and England, 1973). At every catheterisation the bladder was drained as completely as possible. Immediately prior to withdrawal of the catheter, 50 ml of Trisdine were instilled into the bladder and left there.

*Group B. Intermittent catheterisation with the O'Neil catheter.* A sterile, disposable O'Neil catheter, size 14 F, was used for each catheterisation. This consisted of a prelubricated, polyvinyl chloride Nelaton catheter with a special introducer (O'Neil *et al.*, 1982), manufactured by Go Medical Industries Ltd, Subiaco, Western Australia. Catheterisation was carried out according to written instructions for the intermittent catheterisation of male and female patients with the O'Neil catheter. The technique consisted of inserting an introducer into the urethra to the depth of the flange (1.5 cm) and then gently pushing a catheter covered with a plastic bag through the introducer and urethra into the bladder and collecting the urine in the plastic bag.

*Groups A and B.* All catheterisations on male patients were performed by members of the catheter team and all catheterisations on female patients were done by the nursing staff. At every catheterisation a specimen of urine was obtained and cultured on solid media according to standard microbiological techniques. When significant bacteriuria occurred an appropriate antimicrobial agent was given orally or parenterally for 5 days. Patients who were having Trisdine injected into the bladder at the end of each intermittent catheterisation continued to receive Trisdine bladder instillations while an antimicrobial agent was administered systemically.

The method used for classifying the type of neuropathic bladder dysfunction has been described previously (Pearman, 1976). The bladder classification at the time of discharge from hospital of the 30 male patients is shown in Tables 1 and 2. There was a similar distribution of types of neuropathic bladder dysfunction in groups A and B.

### *Criteria*

A diagnosis of significant bacteriuria was made when a catheter specimen of urine showed either (1) $\geqslant 1000$ colony forming units (cfu)/ml with the same species of micro-organism in 3 consecutive specimens when the catheter was passed 6- or 8-hourly, or in 2 consecutive specimens when the catheter was passed 12-hourly, or (2) $\geqslant 10{,}000$ cfu/ml in 1 specimen when the catheter was passed daily.

An episode of significant bacteriuria was considered to have occurred from the time a laboratory diagnosis of significant bacteriuria was made until a 5-day course of an appropriate antibiotic resulted in all catheter specimens of urine being free of the organism for 7 consecutive days. If a relapse occurred, *i.e.* the same micro-organism with the same biogram and same antibiogram was isolated again within 7 days of ceasing the antibiotic, it was considered to be a recurrence of the original episode. If significant bacteriuria occurred more than 7 days after cessation of treatment it was regarded as a new episode, whether it was due to the same species or a different species of micro-organism. Significant bacteriuria caused by a different organism was called a new episode of bacteriuria, irrespective of the time it occurred after a previous episode.

The period of intermittent catheterisation of each patient was defined as the number of days that a patient was intermittently catheterised at least once every 24 h or more frequently.

**Table 1** Duration of Intermittent Catheterisation of Male Patients

| | | *Period of intermittent catheterisation (days)* | | | | | |
|---|---|---|---|---|---|---|---|
| *Group* | *Bladder classification at discharge from hospital* | *13–30* | *31–60* | *61–90* | *91–120* | *121–150* | *Total no of patients* |
| A<br>Nelaton catheter<br>+Trisdine bladder instillation | Normal | 2 | — | — | — | — | 2 |
| | Incomplete UMN* (tetraplegic) | — | 2 | — | — | — | 2 |
| | Complete UMN (tetraplegic) | — | 2 | — | 4 | 1 | 7 |
| | Complete UMN (paraplegic) | — | — | 3 | 2 | — | 5 |
| | Incomplete LMN† | 1 | — | — | — | — | 1 |
| | Complete LMN | — | — | 2 | — | — | 2 |
| Total no. of patients | | 3 | 4 | 5 | 6 | 1 | 19 |
| B<br>Nelaton catheter<br>+introducer<br>(O'Neil) | Normal | — | 1 | — | — | — | 1 |
| | Complete UMN (tetraplegic) | — | 2 | 2 | — | 1 | 5 |
| | Incomplete UMN (paraplegic) | — | — | 1 | — | — | 1 |
| | Complete UMN (paraplegic) | — | 1 | 1 | — | 1 | 3 |
| | Incomplete LMN | 1 | — | — | — | — | 1 |
| Total no. of patients | | 1 | 4 | 4 | — | 2 | 11 |
| | | Up to 120 days = 27 (90%) | | | | More than 120 days = 3 (10%) | |

*Upper motor neurone †Lower motor neurone.

**Table 2** Number of Times Male Patients were Intermittently Catheterised

| | | *Number of catheterisations* | | | | | |
|---|---|---|---|---|---|---|---|
| *Group* | *Bladder classification at discharge from hospital* | *25–100* | *101–200* | *201–300* | *301–400* | *401–500* | *Total no. of patients* |
| A<br>Nelaton catheter + Trisdine bladder instillation | Normal | 2 | — | — | — | — | 2 |
| | Incomplete UMN (tetraplegic) | — | 2 | — | — | — | 2 |
| | Complete UMN (tetraplegic) | — | 2 | 3 | 1 | 1 | 7 |
| | Complete UMN (paraplegic) | — | 3 | 1 | 1 | — | 5 |
| | Incomplete LMN | 1 | — | — | — | — | 1 |
| | Complete LMN | — | 1 | 1 | — | — | 2 |
| Total no. of patients | | 3 | 8 | 5 | 2 | 1 | 19 |
| B<br>Nelaton catheter + introducer (O'Neil) | Normal | 1 | — | — | — | — | 1 |
| | Complete UMN (tetraplegic) | — | 3 | 1 | — | 1 | 5 |
| | Incomplete UMN (paraplegic) | — | 1 | — | — | — | 1 |
| | Complete UMN (paraplegic) | — | 1 | 1 | 1 | — | 3 |
| | Incomplete LMN | 1 | — | — | — | — | 1 |
| Total no. of patients | | 2 | 5 | 2 | 1 | 1 | 11 |
| | | Up to 300 catheterisations = 25 (83%) | | | More than 300 catheterisations = 5 (17%) | | |

The chi-squared contingency table was used to compare the frequency of episodes of significant bacteriuria in different populations.

## Results

### *Duration of intermittent catheterisation and number of catheterisations in male patients*

Tables 1 and 2 show the details of intermittent catheterisation of male patients. Two of the 3 males who regained normal bladder function became catheter-free within 30 days and all 3 required less than 80 catheterisations. The 3 males with incomplete upper motor neurone bladders became catheter-free within 64 days and had less than 183 catheterisations. In contrast, only 5 of the 20 patients with complete upper motor neurone bladders were able to dispense with the need for catheterisation within 60 days and it took 148 days and up to 443 catheterisations for all of those with complete upper motor neurone bladders to become catheter-free. The 2 males with incomplete lower motor neurone bladders became catheter-free within 27 days and each had less than 76 catheterisations. In contrast, the 2 males with complete lower motor neurone bladders were intermittently catheterised for 64 and 67 days (197 and 202 catheterisations). Overall, 27 of the 30 males (90%) were catheterised for up to 120 days (Table 1) and 25 (83%) had up to 300 catheterisations each (Table 2).

### *Duration of intermittent catheterisation and number of catheterisations in female patients*

Group A consisted of 1 patient who regained normal bladder function and was intermittently catheterised for 28 days (64 catheterisations) and 2 paraplegics with complete upper motor neurone bladders who were catheterised for 70 and 173 days (216 and 550 catheterisations). Group B comprised 1 patient who regained normal bladder function who was intermittently catheterised for 10 days (22 catheterisations), 2 tetraplegics with complete upper motor neurone bladders who were catheterised for 66 and 205 days (190 and 494 catheterisations) and 1 patient with an incomplete lower motor neurone bladder who was catheterised for 24 days (80 catheterisations).

### *Incidence of significant bacteriuria during intermittent catheterisation of male patients*

*Group A (Nelaton catheter with Trisdine bladder instillation).* Nine male patients had no significant bacteriuria during the period of intermittent catheterisation, 3 patients had 1 episode, 4 patients each had 2 episodes, 2 patients each had 3 episodes and 1 patient had 5 episodes, giving a total of 22 episodes of significant bacteriuria in this group. In all, 3764 catheterisations were performed on the 19 males in group A. The average incidence of significant bacteriuria was 1/171 catheterisations, *i.e.* overall 0.58% of catheterisations resulted in an episode of significant bacteriuria in the group A male patients.

*Group B (O'Neil catheter)*. Two male patients had no significant bacteriuria during the period of intermittent catheterisation, 3 patients had 1 episode, 3 patients each had 2 episodes, 1 patient had 3 episodes and 2 patients each had 7 episodes, resulting in a total of 26 episodes of significant bacteriuria in this group. In all, 2236 catheterisations were done on the 11 males in group B. The average incidence of significant bacteriuria was 1/86 catheterisations, *i.e.* overall 1.16% of catheterisations resulted in an episode of significant bacteriuria in the group B male patients.

In male patients the use of a Nelaton catheter with the instillation of Trisdine into the bladder at the end of each catheterisation resulted in a mean incidence of significant bacteriuria of 0.58% per catheterisation, which was one-half of that observed when the O'Neil catheter was used (1.16%) and the difference was significant ($P = 0.02$).

### *Incidence of significant bacteriuria during intermittent catheterisation of female patients*

*Group A (Nelaton catheter with Trisdine bladder instillation)*. Two of the 3 female patients each had 1 episode of significant bacteriuria and the other had 2 episodes, giving a total of 4 episodes of significant bacteriuria; 830 catheterisations were carried out on these women. The average incidence of significant bacteriuria was 1/208 catheterisations, *i.e.* overall 0.48% of catheterisations resulted in an episode of significant bacteriuria in female patients of group A.

*Group B (O'Neil catheter)*. Each of the 4 female patients in group B individually had 2, 5, 7 and 9 episodes of significant bacteriuria, producing a total of 23 episodes in this group; 786 catheterisations were done on these patients. The average incidence of significant bacteriuria was 1/34 catheterisations, *i.e.* overall 2.93% of catheterisations resulted in an episode of significant bacteriuria in the group B female patients.

The mean incidence of significant bacteriuria in the female patients who received Trisdine instillations was 0.48%, which was only one-sixth of that observed in female patients who were intermittently catheterised with the O'Neil catheter (2.93%). This difference was highly significant ($P < 0.001$).

### *Micro-organisms which caused significant bacteriuria during intermittent catheterisation of male patients*

The micro-organisms cultured from the catheter specimens of urine of male patients while they were being intermittently catheterised are listed in Table 3.

On 2 occasions the first positive culture in an episode of significant bacteriuria contained 2 organisms which were both present in significant numbers and remained in significant numbers throughout the episode. It was considered that each of these episodes was caused by both the organisms

**Table 3** Micro-organisms which Caused Significant Bacteriuria During Intermittent Catheterisation of Male Patients

| *Group* | *Micro-organism* | *No of episodes of significant bacteriuria* |
|---|---|---|
| A<br>Nelaton catheter<br>+ Trisdine<br>bladder<br>instillation | Gram-negative | |
| | *Klebsiella pneumoniae* | 10 |
| | *Pseudomonas aeruginosa* | 3 |
| | *Proteus mirabilis* | 2 |
| | *Acinetobacter calcoaceticus* | 1 |
| | *Providencia rettgeri* | 1 |
| | *Serratia marcescens* | 1 |
| | *P. aeruginosa + P mirabilis* | 1 |
| | Gram-positive | |
| | *Streptococcus faecalis* | 3 |
| | Total | 22 |
| B<br>Nelaton<br>catheter<br>+ introducer<br>(O'Neil) | Gram-negative | |
| | *Klebsiella pneumoniae* | 9 |
| | *Proteus mirabilis* | 3 |
| | *Escherichia coli* | 2 |
| | *Pseudomonas aeruginosa* | 2 |
| | *Acinetobacter calcoaceticus* | 1 |
| | *Providencia stuartii* | 1 |
| | Gram-positive | |
| | *Streptococcus faecalis* | 5 |
| | *Staphylococcus epidermidis* | 1 |
| | *Corynebacterium jeikeum* | 1 |
| | Gram-negative + Gram-positive | |
| | *P. mirabilis + S. faecalis* | 1 |
| | Total | 26 |

concerned; *Pseudomonas aeruginosa* and *Proteus mirabilis* on 1 occasion and *P. mirabilis* and *Streptococcus faecalis* on the other (Table 3).

Gram-negative bacteria were responsible for most of the episodes of significant bacteriuria in both groups of males. These organisms caused 19 (86%) of the 22 episodes which occurred in those who had Trisdine instilled into the bladder. Gram-negative bladder also caused 19 (73%) of the 26 episodes in males who were catheterised with the O'Neil catheter. One Gram-negative organism, *Klebsiella pneumoniae*, was responsible for almost one-half (10/22) of the episodes in males who had received Trisdine and for just over one-third (9/26) of the episodes in those in whom the O'Neil catheter was used (Table 3).

Gram-positive bacteria (mainly *S. faecalis*) were isolated in 8 (31%) of the 26 episodes of significant bacteriuria which occurred when the O'Neil catheter was used, but in only 3 (14%) of the 22 episodes when Trisdine was instilled, although the trend was not statistically significant.

### *Micro-organisms which caused significant bacteriuria during intermittent catheterisation of female patients*

The micro-organisms cultured from the catheter specimens of urine of female patients while they were being intermittently catheterised are listed in Table 4.

**Table 4** Micro-organisms which Caused Significant Bacteriuria During Intermittent Catheterisation of Female Patients

| *Group* | *Micro-organism* | *No. of episodes of significant bacteriuria* |
|---|---|---|
| A<br>Nelaton catheter + Trisdine bladder instillation | Gram-negative | |
| | *Klebsiella pneumoniae* | 3 |
| | *Proteus mirabilis* | 1 |
| | Total | 4 |
| B<br>Nelaton catheter + introducer (O'Neil) | Gram-negative | |
| | *Klebsiella pneumoniae* | 8 |
| | *Escherichia coli* | 5 |
| | *Pseudomonas aeruginosa* | 3 |
| | *Enterobacter cloacae* | 1 |
| | *Morganella morganii* | 1 |
| | *Providencia stuartii* | 1 |
| | Gram-positive | |
| | *Streptococcus faecalis* | 3 |
| | Yeast | |
| | *Candida albicans* | 1 |
| | Total | 23 |

Similar types of organisms were responsible for the episodes of significant bacteriuria in males and females. Gram-negative bacteria caused all of the episodes which occurred in women who received Trisdine and 19 (83%) of the 23 episodes in those who were catheterised with the O'Neil catheter. One Gram-negative organism, *K. pneumoniae*, was responsible for 3 of the 4 episodes in females who had received Trisdine and for just over one-third (8/23) of the episodes in those in whom the O'Neil catheter was used (Table 4).

Gram-positive bacteria (*S. faecalis*) caused 3 (13%) of the 23 episodes of significant bacteriuria in females when the O'Neil catheter was used, but did not cause a single episode in those who had Trisdine instillations. The absence of Gram-positive bacteria as a cause of significant bacteriuria in females who had received Trisdine showed a trend in the same direction as in males who had received this disinfectant, but the total number of female patients was too small for this trend to be statistically significant.

## Discussion

All of the catheterisations were carried out by members of the staff. The use of the O'Neil catheter in males resulted in an incidence of bacteriuria of 1.16% per catheterisation. This was not significantly different from the incidence of 1.43% associated with the use of a Nelaton catheter in males without instillation of an antibacterial solution into the bladder as reported by Pearman (1979). The incidence of bacteriuria produced by the O'Neil catheter in females of 2.93% per catheterisation was similar to that reported by O'Neil *et al.* (1982), where 2 of 52 females (3.85%) catheterised by this technique developed bacteriuria. As with males, the incidence of bacteriuria in females catheterised by the O'Neil catheter was not significantly different from the incidence of 2.48% which occurred when females were intermittently catheterised with a Nelaton catheter without instillation of an antibacterial solution into the bladder (Pearman, 1979). It is concluded that the O'Neil catheter does not reduce the incidence of significant bacteriuria compared with a Nelaton catheter during intermittent catheterisation of both males and females following acute spinal cord trauma.

The results of the present study have shown that the use of the O'Neil catheter during intermittent catheterisation in the acute phase after spinal cord injury was associated with a significantly higher incidence of bacteriuria in both males and females compared with the routine instillation of 50 ml of a mild disinfectant solution (Trisdine) into the bladder after each passage of a Nelaton catheter. Nevertheless, the O'Neil catheter has certain features which may make it advantageous in other circumstances. It is marketed in a sterile plastic bag which protects the catheter and enables it to be inserted aseptically without having to use a conventional catheter pack to create a sterile field. The plastic bag also conveniently collects the urine. The time required to perform each catheterisation is reduced because the operator does not need to put on a sterile gown or place sterile drapes on the patient. The O'Neil catheter may be useful for individuals practising intermittent self-catheterisation. It has been shown that acute traumatic paraplegics who have reached the stage of sitting up can cease being catheterised by the staff and can achieve good results by intermittently catheterising themselves (Wyndaele and De Taeye, 1990). Sufficiently large trials of the O'Neil catheter are needed in patients other than those with acute spinal cord trauma to determine the incidence of bacteriuria associated with its use in each group, but as far as we are aware this has not yet been done.

The normal resident bacteria in the lower end of the urethra are the main cause of bladder infection due to passage of a catheter up the urethra. Even when a sterile instrument is passed with faultless aseptic technique it is impossible to do so without carrying some urethral organisms into the bladder at the same time. The O'Neil catheter attempts to bypass the lower urethral flora by inserting a protective sheath into the distal 1.5 cm of the urethra before passing the catheter through it. However, insertion of any mechanical device into the urethra unavoidably carries bacteria up the urethra and some of these are picked up by the catheter as it leaves the sheath. The inevitability of this microbial contamination is demonstrated by the results of the present study, which showed that the O'Neil catheter did not reduce the incidence of bacteriuria in males or females compared with a previous trial where a Nelaton catheter was used without instillation of an antibacterial solution into the bladder (Pearman, 1979). Furthermore, the study reported here agrees with the observations of Gillespie *et al.* (1962) that efforts to reduce urethral contamination are not as effective as disinfection of the bladder after passage of the catheter in reducing the incidence of urinary tract infection following catheterisation.

The instillation of 50 ml of Trisdine into the bladder at the end of each catheterisation substantially reduced the incidence of significant bacteriuria due to both Gram-negative and Gram-positive organisms. However, Trisdine appeared to be more effective against Gram-positive bacteria in both males and females, as was also observed in the previous study (Pearman *et al.*, 1988). Laboratory studies have shown that Gram-negative bacteria are generally more susceptible to Trisdine *in vitro* than most Gram-positive organisms (Harper, 1983; Harper and Epis, 1987). Some of the Gram-negative isolates from patients receiving Trisdine in this study were tested against Trisdine *in vitro* and were found to be susceptible. However, it appears that prophylactic instillations of Trisdine into the urinary bladder are clinically more effective against Gram-positive than Gram-negative bacteria. The increased resistance of Gram-negative bacteria to Trisdine in the urinary bladder may be due to the protective effect of the polysaccharide glycocalyx which these organisms secrete around themselves when growing in urine (Stickler *et al.*, 1987).

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# Flexible Cystoscopy Compared with Ultrasound in the Detection of Recurrent Bladder Tumours

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Summary—A combination of transrectal and transabdominal ultrasound was compared with flexible cystoscopy as a means of detecting recurrent bladder tumours. The study group comprised 50 patients who had previously had rigid cystoscopy. They underwent combination ultrasound in the out-patient department 1 week before flexible cystoscopy. Combination ultrasound identified 25 patients with recurrent tumours and flexible cystoscopy identified 26.

Thirty-four patients (68%) preferred ultrasound, 10 (20%) preferred flexible cystoscopy, 3 (6%) preferred general anaesthesia and rigid cystoscopy and 3 (6%) had no preference. The main objection to ultrasound was the use of the transrectal probe.

Check cystoscopy in patients with recurrent bladder tumours creates a large urological workload. To date, rigid cystoscopy has been the main method of follow-up but flexible cystoscopy is becoming increasingly popular because it can be carried out under local anaesthesia on an out-patient basis (Clayman *et al.*, 1984; Fowler *et al.*, 1984; Powell *et al.*, 1984). However, it does involve instrumentation of the genitourinary system and complications have been reported (Fowler, 1984; Flannigan *et al.*, 1988). Davies *et al.* (1989a and b, 1990) showed that combination ultrasound is an effective alternative procedure in the follow-up of recurrent bladder tumours.

The aim of the present study was to correlate the detection rates of recurrent tumours by combination ultrasound and by flexible cystoscopy in patients who had previously undergone rigid cystoscopy and to assess which procedure they preferred.

## Patients and Methods

The series comprised 50 patients (37 males, 13 females) with a mean age of 65 years (range 48–72) and with known bladder tumours who had previously undergone rigid cystoscopy. They underwent combination ultrasound in the out-patient department 1 week before flexible cystoscopy.

Transabdominal and transrectal ultrasound examinations were performed with a Bruel & Kjaer ultrasound machine (type 1846) with a 4MHz abdominal probe and a 7MHz transrectal probe giving longitudinal scans.

Flexible cystoscopy was performed in the day surgery unit using 1% lignocaine gel and an Olympus CYF flexible cystoscope. All personnel performing the investigations had previous experience in using the techniques.

Between 2 and 4 weeks after undergoing cystoscopy the patients were sent a questionnaire asking them to place the 3 procedures in order of preference.

## Results

Combination ultrasound detected tumour recurrence in 25 patients and flexible cystoscopy identified it in 26. A small 2-mm tumour, located on the posterior wall of the bladder, was missed in 1 patient using ultrasound. Thus there was an excellent correlation rate between the 2 modalities.

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**Table 1** Procedures According to Preference

| | *First choice (%)* | *Second choice (%)* | *Third choice (%)* |
|---|---|---|---|
| Ultrasound | 34 (68) | 10 (20) | 3 (6) |
| Flexible cystoscopy | 10 (20) | 35 (70) | 2 (4) |
| Rigid cystoscopy | 3 (6) | 2 (4) | 42 (84) |
| No preference | 3 (6) | 3 (6) | 3 (6) |

The false positive rate for ultrasound was 2%.

All 50 patients replied to the questionnaire (Table 1). Combination ultrasound was the preferred method in 68%, followed by flexible cystoscopy. Rigid cystoscopy was favoured by very few. Three patients experienced discomfort with the use of the rectal probe.

## Discussion

This study confirms our previous finding that a combination of transabdominal and transrectal ultrasound can be used in the out-patient department to detect recurrent bladder tumours (Davies *et al.*, 1990). It must be remembered that flexible cystoscopy, although representing an advance on rigid cystoscopy, still has some degree of morbidity (Fowler, 1984; Flannigan *et al.*, 1988) and the latter workers showed that patients preferred flexible to rigid cystoscopy, with only 11% favouring rigid cystoscopy under general anaesthesia.

In our previous study (Davies *et al.*, 1990) only 1 patient preferred follow-up with rigid cystoscopy to ultrasound.

This study has shown that, when comparing rigid cystoscopy, flexible cystoscopy and combination ultrasound, the latter is the most popular method. The good correlation between the detection rates is encouraging. However, as previously shown (Davies *et al.*, 1989a and b, 1990), combination ultrasound does not detect all tumour recurrences. However, those that were missed were less than 2 mm in diameter and it could be argued that such small tumours are not significant. The initial financial outlay for ultrasound equipment is greater than that required for flexible cystoscopy (Table 2). However, ultrasound has many other urological applications and so its purchase price cannot be directly compared with that of a flexible cystoscope.

In conclusion, we have demonstrated a good correlation between combination ultrasound and flexible cystoscopy in the detection of recurrent bladder tumours and have shown that most patients prefer ultrasound.

It is suggested that combination ultrasound has a useful role to play in the follow-up of recurrent bladder tumours and that a sensible policy to adopt in the first instance would be to alternate between ultrasound and flexible cystoscopy in the follow-up of these patients.

**Table 2** Cost* of Ultrasound and Cystoscopy Equipment

| *Ultrasound* | £ |
|---|---|
| Bruel & Kjaer machine (type 1846) | 28,000 |
| 7MHz transrectal probe | 9,021 |
| 4MHz abdominal probe | 5,760 |
| Total | 42,781 |
| Cystoscope | |
| Olympus CYF flexible cystoscope | 6,500 |
| Light source | 2,385– 7,305 |
| Total | 8,885–13,805 |

*As on 1 August 1990.

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# Comparison of alpha$_1$ Adrenoceptors in the Prostate Capsule of Men with Symptomatic and Asymptomatic Benign Prostatic Hyperplasia

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Summary—The objective of this study was to compare the binding and functional properties of alpha$_1$ adrenoceptors in prostate capsules obtained from men with symptomatic and asymptomatic benign prostatic hyperplasia (BPH) undergoing simple retropubic prostatectomy and cystoprostatectomy respectively. Saturation experiments using $^{125}$I-Heat demonstrated that the density and binding affinity of alpha$_1$ adrenoceptors in the prostate capsules obtained from men with symptomatic and asymptomatic BPH were similar. Non-cumulative dose response experiments using phenylephrine demonstrated that the magnitude of the contractile response to phenylephrine was 4-fold greater in the prostate capsules from men with symptomatic BPH than from those with asymptomatic BPH. The $EC_{50}$ of phenylephrine in the prostate capsules of men with symptomatic and asymptomatic BPH was similar. A correlation between alpha$_1$ adrenoceptor density and phenylephrine $E_{max}$ was not observed, implying that either alpha$_1$ adrenoceptors are not localised exclusively to the prostate smooth muscle or that spare alpha$_1$ adrenoceptors exist. This study suggests that the neuropharmacological properties of the prostate capsule may play a significant role in the development of infravesical obstruction in the ageing male population.

The clinical manifestations of benign prostatic hyperplasia are related entirely to bladder outlet obstruction (Walsh, 1986). Caine (1986) proposed that infravesical obstruction in men with symptomatic BPH is composed of static and dynamic factors. The static component of obstruction is related primarily to the mechanical obstruction caused by the enlarging prostate adenoma. The dynamic component is determined primarily by the tone of the prostate smooth muscle. The contractile properties of the prostate adenoma and prostate capsule smooth muscle are mediated primarily by alpha$_1$ adrenoceptors (Hedlund *et al.*, 1985; Hiebele *et al.*, 1986; Lepor *et al.*, 1988).

The specific features of the prostate adenoma predisposing to the development of bladder outlet obstruction are poorly understood. We have used radioligand receptor binding assays (Gup *et al.*, 1990) and *in vitro* contractile studies (Gup *et al.*, 1989) to compare the binding and functional properties of alpha$_1$ adrenoceptors in prostate adenomas obtained from men with symptomatic and asymptomatic BPH in order to clarify the role of alpha adrenoceptors in the development of infravesical obstruction. The density ($B_{max}$) and binding affinity ($K_d$) of alpha$_1$ adrenoceptors in these adenomas are similar (Gup *et al.*, 1990). The magnitude of the maximal contractile response ($E_{max}$) to phenylephrine and the potency ($EC_{50}$) of phenylephrine for inducing contractions in prostate adenomas obtained from men with symptomatic and asymptomatic BPH are also similar (Gup *et al.*, 1989). These studies indicate that the development of symptomatic BPH is not related to alterations in the binding or functional properties of alpha$_1$ adrenoceptors in the prostate adenoma.

It is conceivable that the tone of the prostate capsule influences prostatic urethral resistance by encroaching upon the enlarging prostate adenoma. The present study was designed to characterize the

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binding and functional properties of alpha$_1$ adrenoceptors in the human prostate capsule. The properties of alpha$_1$ adrenoceptors were compared in prostate capsules obtained from men with symptomatic and asymptomatic BPH in order to determine whether infravesical obstruction in men with BPH was associated with changes in the binding and functional properties of alpha$_1$ adrenoceptors in the prostate capsule.

## Materials and Methods

### *Source of tissue specimens*

Prostate capsule specimens were obtained from 9 males with asymptomatic BPH undergoing cystoprostatectomy and 11 males with symptomatic BPH undergoing simple retropubic prostatectomy. A standardised quantitative symptom score analysis was used to evaluate obstructive voiding symptoms pre-operatively (Boyarsky *et al.*, 1977). Maximum urinary flow rates were determined preoperatively using a Dantec Urodyn 1000 flow meter. The obstructive symptom scores and urinary flow rates documented the absence of bladder outlet obstruction in men undergoing cystoprostatectomy and confirmed the presence of bladder outlet obstruction in those undergoing simple retropubic prostatectomy (Table 1). The prostate capsule specimens from men undergoing simple retropubic prostatectomy were obtained from the capsular tissue adjacent to the anterior capsulotomy. The prostate capsule specimens from men undergoing cystoprostatectomy were obtained from the anterior aspect of the surgical capsule. Tissues for radioligand receptor binding studies were immediately frozen at −70°C. BPH was confirmed histologically by a staff pathologist in the prostate adenomas obtained from all men undergoing cystoprostatectomy and retropubic prostatectomy.

### *Radioligand receptor binding methods*

*Preparation of tissue homogenates.* Prostate specimens were immersed in liquid nitrogen and pulverised with a Thermovac tissue pulveriser (Redi-Industries Corporation). The pulverised tissues were homogenised in 20 volumes of ice-cold 5 mM potassium phosphate buffer (pH 7.4) with a Brinkman Polytron (Pt-10-35) at a speed setting of 6 for 60 s. The homogenates were centrifuged at 40 000 g for 10 min at 4°C. The pellets were homogenised in 20 volumes of Krebs-Ringers phosphate buffer (pH 7.4 at 25°C) containing 100 μM sodium-guanosine triphosphate (Sigma Chemical Company). The homogenates were gently shaken on a gyratory shaker (New Brunswick Corporation) at room temperature for 30 min and centrifuged at 40 000 g for 10 min at 4°C. The pellets were washed twice with 20 volumes of 50 mM sodium potassium phosphate buffer at 4°C (pH 7.4), homogenised and centrifuged at 40 000 g for 10 min at 4°C. The final pellets were homogenised in 50 volumes of 50 mM sodium potassium phosphate buffer (pH 7.4) at room temperature and filtered through fine Nitex mesh gauze.

*Saturation analysis: alpha$_1$ adrenoceptors.* Saturation analyses were performed at 7 different concentrations (0.01 nM–0.40 nM) of $^{125}$I-Heat (2-4-hydroxyphenylethylaminoethyl tetralone) at constant specific activity (2000 Ci/mmol) (New England Nuclear Corporation). Homogenates of prostate capsule were obtained from 6 males undergoing cystoprostatectomy and 7 males undergoing simple retropubic prostatectomy. Total binding was determined in 500 μl containing 400 μl tissue homogenate, 50 μl of 50 mM sodium potassium phosphate buffer (pH 7.4), and 50 μl of $^{125}$I-Heat at varying concentrations. Total and nonspecific binding determinations for each $^{125}$I-Heat concentration were performed in triplicate in polypropylene test tubes. The assay tubes were shaken on a New Brunswick gyratory shaker for 30 min at room temperature. The binding assays were terminated by filtering over Schleicher and Schuell no. 32 2.4 cm glass fibre filters on a 45-well vacuum manifold. The glass filter discs were washed 4 times with 4 ml ice-cold 50 mM sodium potassium phosphate buffer (pH 7.4) containing 10% w/v polyethylene glycol (molecular weight approximately 3350) (Sigma Chemical Company) under vacuum suction. The glass filter discs were placed in 10 ml aqueous accepting scintillation fluid (Budget-Solve, RPI) and allowed to equilibrate at room temperature for at least 8 h. The scintillation vials were then counted on a Beckman LS-3801 liquid scintillation counter at a calculated average efficiency of 50%. Saturation curves, Scatchard plots, $K_d$, $B_{max}$, and the linear correlation coefficients (LCO) of the observed Scatchard plots were generated by a computer program.

### *In vitro contractile studies*

*Tissue preparation.* The prostate capsules were immediately placed in cold oxygenated (5% $CO_2$ and 95% $O_2$) Krebs solution of the following composition: NaCl 130 mM; $NaHCO_3$; KCl 5 mM; $NaH_2PO4$ 1.2 mM; $MgSO_4$ 1.2 mM; $CaCl_2$

2.5 mM; dextrose 11.4 mM. The prostate tissue was cut into longitudinal strips approximately 2 to 4 mm wide by 15 mm in length. The strips were suspended in 50-ml organ baths containing Krebs buffer. The baths were maintained at 37°C and oxygenated with 5% $CO_2$ and 95 $O_2$. Isometric tension was measured with a Grass Instruments FTO3 force transducer coupled to a SensorMedics Dynograph recorder. At the completion of each experiment the tissue strips were blotted on filter paper and weighed.

*Contractile experiments: phenylephrine.* Phenylephrine non-cumulative concentration response experiments were performed on prostate capsules obtained from 8 men undergoing simple retropubic prostatectomy and 5 men undergoing cystoprostatectomy. The contractile responses (gm) were determined at varying concentrations of phenylephrine (10-7M to 10-4M). The concentration of phenylephrine producing 50% of the maximal contractile response (EC$_{50}$) and the maximal response to phenylephrine (E$_{max}$) were determined for the prostate adenomas.

## Results

Quantitative assessment of obstructive voiding symptoms and maximum urinary flow rates were determined pre-operatively for 9 patients with transitional cell carcinoma of the bladder undergoing cystoprostatectomy and 11 patients with symptomatic BPH undergoing simple retropubic prostatectomy. Their mean age, obstructive voiding score (maximum score = 15) and maximum urinary flow rate are summarised in Table 1. The mean ages of patients in both groups were similar ($P$ = 0.57). The quantitative symptom score assessment formulated by Boyarsky *et al.* (1977) was used to quantitate the obstructive voiding symptoms. The mean obstructive voiding score for the men undergoing simple retropubic prostatectomy was 3.5 times greater than that of the men undergoing prostatectomy ($P$ = 0.0003) (Table 1). Ten of the 11 men undergoing simple retropubic prostatectomy presented with urinary retention and subsequently failed voiding trials; the mean peak urinary flow rate was, therefore, negligible for these patients. The mean peak urinary flow rate for men undergoing cystoprostatectomy was 22 ml/s. These findings indicate that this study was appropriately designed to compare the binding and functional properties of alpha$_1$ adrenoceptors in the prostate capsules of age-matched men with symptomatic and asymptomatic BPH.

**Table 1** Source of Prostate Specimens

| *Source* | *No.* | *Age (years)* | *Obstructive symptom score* | *Maximum flow rate (ml/s)* |
|---|---|---|---|---|
| *Asymptomatic BPH* (cystoprostatectomy) | 9 | 69 ± 2 | 2.3 ± 0.9 | 22 ± 7 |
| *Symptomatic BPH* (retropubic prostatectomy) | 11 | 71 ± 2 | 8.0 ± 0.9 | 0* |
| *P* | | 0.57 | 0.0003 | — |

The ages, obstructive symptom scores and maximum urinary flow rates are expressed as mean ± SEM.

* The mean maximum flow rate for men with symptomatic BPH was 0 since 10 of 11 men presented in urinary retention and subsequently failed voiding trials.

Saturation experiments using $^{125}$I-Heat were performed on homogenates of prostate capsules obtained from 6 men undergoing cystoprostatectomy and 7 men undergoing simple retropubic prostatectomy. The Scatchard plots were linear, indicating a single population of high affinity $^{125}$I-Heat binding sites (Fig. 1). The mean equilibrium dissociation constants (K$_d$) in the prostate capsules from men with symptomatic and asymptomatic BPH were similar (Table 2), as was mean density of $^{125}$I-Heat binding sites (B$_{max}$), expressed as fmol/mg wet wt ($P$ = 0.27) (Table 2). The saturation studies indicated that the alpha$_1$ adrenoceptor binding sites in the prostate capsules were homogeneous and that the densities of alpha$_1$ adrenoceptors were similar.

Phenylephrine non-cumulative concentrations response experiments were performed on prostate capsules obtained from 8 males undergoing simple retropubic prostatectomy and 5 males undergoing cystoprostatectomy. The composite concentration response curves for phenylephrine indicated that the contractile responses were saturable (Fig. 2). The mean phenylephrine E$_{max}$ observed in prostate capsules obtained from men undergoing simple retropubic prostatectomy was 4-fold greater than that observed in capsules obtained from men undergoing cystoprostatectomy (Table 3). This difference approached statistical significance ($P$ = 0.11). The development of symptomatic bladder outlet obstruction in men with BPH may be related to the contractile properties of the prostate capsule. The mean phenylephrine EC$_{50}$ determined in the prostate capsules obtained from men undergoing cystoprostatectomy and simple retropubic prostat-

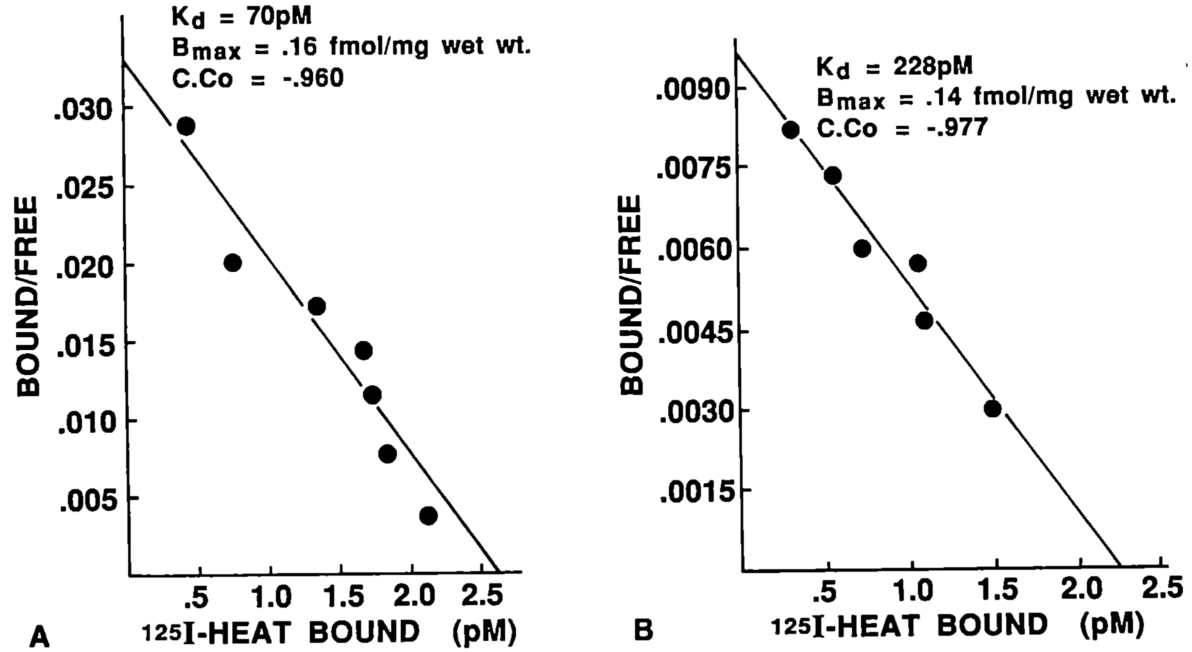

**Fig. 1** Representative Scatchard plots of $^{125}$I-Heat binding in prostate capsule homogenates obtained from men with symptomatic BPH undergoing simple retropubic prostatectomy (A) and cystoprostatectomy (B).

ectomy was similar, indicating that the development of infravesical obstruction in men with symptomatic BPH was not related to increased sensitivity of these alpha$_1$ adrenoceptor binding sites.

## Discussion

The primary objective of the current study was to characterise the binding and functional properties of alpha$_1$ adrenoceptors in prostate capsules obtained from men with symptomatic and asymptomatic BPH. The capsules were obtained from men undergoing simple retropubic prostatectomy and cystoprostatectomy. Quantitative symptom score analysis and measurement of maximum urinary flow rates indicated that men undergoing cystoprostatectomy had asymptomatic BPH, whereas those undergoing simple retropubic prostatectomy had symptomatic BPH. The prostate specimens were obtained from the anterior region of the surgical capsules. Anterior capsules were characterised since other regions of the prostate are inaccessible during simple retropubic prostatectomy.

**Table 2** $^{125}$I-Heat Binding in Human Prostate Capsules

| *Source* | *No.* | *Equilibrium dissociation constant ($K_d$) pM* | *Receptor density ($B_{max}$) fmol/mg wet wt* |
|---|---|---|---|
| Cystoprostatectomy | 6 | 124±19 | 0.13±0.04 |
| Retropubic prostatectomy | 7 | 129±15 | 0.19±0.02 |
| *P* | | 0.80 | 0.27 |

$K_d$ and $B_{max}$ are expressed as mean ± SEM.

The present study describes the first characterisation of alpha$_1$ adrenoceptors in the prostate capsule using radioligand receptor binding assays. The binding of $^{125}$I-Heat in prostate capsules was consistently saturable and of high affinity. The Scatchard plots were linear, indicating homogeneity of these alpha$_1$ adrenergic binding sites. Overall, the equilibrium dissociation constant and density of $^{125}$I-Heat binding sites in prostate capsules were similar to values recently reported for human prostate adenomas (Gup *et al.*, 1990). The binding affinity and density of alpha$_1$ adrenoceptors in the prostate capsules obtained from men with symptomatic and asymptomatic BPH in the present study were similar. The development of infravesical obstruction does not appear to be related to increased levels of alpha$_1$ adrenoceptors in the prostate capsule.

Caine *et al.* (1975) observed that the human

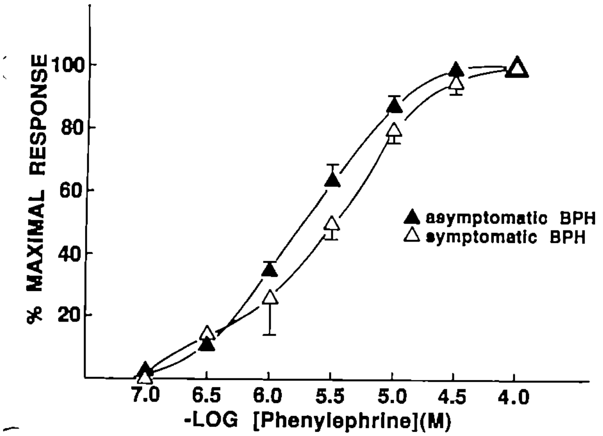

**Fig. 2** Individual phenylephrine concentration response experiments were performed on strips of prostate capsules from 8 males undergoing simple retropubic prostatectomy (▲▲) and 5 males undergoing cystoprostatectomy (△△). The composite curves for the phenylephrine dose response experiments in the prostate capsules are illustrated.

prostate capsule contracts in the presence of norepinephrine, a non-selective alpha agonist. We found that the capsule contracts in the presence of phenylephrine, a selective alpha$_1$ adrenoceptor agonist. The magnitude of the contractile response to phenylephrine in the prostate capsules obtained from men undergoing simple retropubic prostatectomy was 4 times greater than that observed in capsules obtained from men undergoing cystoprostatectomy. The difference in the phenylephrine $E_{max}$ approached statistical significance ($P=0.11$). The development of symptomatic BPH may be associated with an enhanced responsiveness of the prostate capsules to alpha$_1$ adrenergic agonists. It is therefore conceivable that the tone of the prostate capsule is a significant factor in the development of bladder outlet obstruction.

The magnitude of the contractile response to phenylephrine in the prostate capsules obtained from men undergoing simple retropubic prostatectomy and cystoprostatectomy was markedly different despite equivalent levels of alpha$_1$ adrenoceptors. Therefore the density of alpha$_1$ adrenoceptors in prostate capsules is not proportional to the magnitude of the contractile response of the prostate capsule to alpha$_1$ adrenergic stimulation. It is conceivable that alpha$_1$ adrenoceptors are not localised exclusively to the smooth muscle component of the prostate. Alpha$_1$ adrenoceptors associated with vascular smooth muscle, epithelial secretory cells and fibroblasts would not contribute to a contractile response following phenylephrine stimulation. Autoradiographic studies have demonstrated that muscarinic cholinergic receptors are localised exclusively to the epithelial component of the prostate adenoma (Lepor and Kuhar, 1984). Chapple *et al.* (1989) suggested that alpha$_1$ adrenoceptors were associated with the prostate stroma. Autoradiographic localisation of prostate alpha$_1$ adrenoceptors to the individual components of the prostate stroma would further clarify the role of alpha$_1$ adrenoceptors in the prostate.

**Table 3** Contractile Properties of Human Prostate Capsules

| *Source* | *No* | $E_{max}$ *(gm/gm tissue)* | $EC_{50}$ *(μM)* |
|---|---|---|---|
| Cystoprostatectomy | 5 | 22.8±7.1 | 2.2±1.1 |
| Retropubic prostatectomy | 8 | 86.6±35.0 | 2.1±0.4 |
| *P* | | 0.11 | 0.88 |

The maximal contractile response ($E_{max}$) to phenylephrine and the $EC_{50}$ for phenylephrine-induced contractions are expressed as mean ± SEM.

Although 85% of men develop histological evidence of benign prostatic hyperplasia by the eighth decade of life (Berry *et al.*, 1984), only 20% of 50-year-old men will require a prostatectomy for relief of bladder outlet obstruction (Birkhoff, 1983). The discrepancy between the prevalence of BPH and the development of symptomatic bladder outlet obstruction indicates that prostatic enlargement is not the primary parameter leading to infravesical obstruction in the ageing male population. It is difficult to imagine that a single factor determines whether BPH will be associated with infravesical obstruction. The smooth muscle and collagen content, the neural innervation, and specific neurotransmitter and neuroreceptor densities associated with the smooth muscle component of the prostate adenoma are likely to be factors predisposing to the development of bladder outlet obstruction. The present study suggests that the neuropharmacological properties of the prostate capsule may also play a significant role in the development of infravesical obstruction in the ageing male population.

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# Indoramin in the Treatment of Prostatic Bladder Outflow Obstruction

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Summary—A series of 40 patients took part in a double-blind, placebo-controlled trial of indoramin in prostatic bladder outflow obstruction. Patients were assessed clinically and urodynamically before and after 4 weeks' treatment. Significant improvement was seen in nocturia, volume voided, flow rates and residual urine. The drug was well tolerated, although 7 patients on treatment and 7 on placebo noted side effects.

These results suggest that indoramin may be a useful agent in the symptomatic management of bladder outflow obstruction.

A non-surgical treatment for prostatic bladder outflow obstruction remains desirable. The demonstration of significant levels of $\alpha$-adrenoreceptors in the stroma and capsule of the hyperplastic prostate (Caine *et al.*, 1975) and the concept that prostatic obstruction consists of static (anatomical) and dynamic (neuropharmacologically mediated) components have led to the use of $\alpha$-adrenoreceptor blocking agents in the treatment of this condition. One of the first drugs to be used was phenoxybenzamine. Double-blind studies of this agent showed a statistically significant improvement in frequency, poor stream, flow rate and other urodynamic parameters (Caine *et al.*, 1978; Gerstenberg *et al.*, 1980; Abrams *et al.*, 1982). Furthermore, Abrams *et al.* (1982) showed that phenoxybenzamine significantly reduced the height and area of the prostatic plateau as measured by urethral pressure profilometry. However, the use of phenoxybenzamine was associated with side effects in up to 30% of patients and in 10% these were severe enough to warrant cessation of treatment. More recently, animal studies have suggested that phenoxybenzamine may cause gastric neoplasia and it is no longer used in the UK to treat bladder outflow obstruction.

Some of the side effects of non-selective $\alpha$-blocking agents such as phenoxybenzamine are due to increased levels of circulating nor-adrenaline, as they block both $\alpha_1$ receptors on the target smooth muscle cell and also $\alpha_2$ receptors on the parent nerve cell, leading to increased release of nor-adrenaline, some of which escapes into the circulation. The use of selective blocking agents such as indoramin, which preserve the $\alpha_2$ mediated negative feedback loop, should therefore be associated with a lower incidence of side effects. Therapeutic efficacy should not be impaired because $\alpha_1$ receptors (rather than $\alpha_2$) are thought to predominate on the smooth muscle cells of the prostate.

We have recently conducted a placebo-controlled, double-blind trial of indoramin in the treatment of bladder outflow obstruction.

## Patients and Methods

The study group comprised 40 patients with bladder outflow obstruction due to benign prostatic enlargement, subsequently confirmed by urodynamics. Patients who had previously undergone prostatic surgery, those with significant cardiovascular disease and those who were on medication likely to affect vesicourethral function or to interact with indoramin were excluded. Informed consent was obtained.

All patients initially received 2 weeks' treatment

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**Table 1** Results (Data are means unless otherwise indicated)

| | Indoramin | | Placebo | | |
|---|---|---|---|---|---|
| | *Week 0* | *Week 4* | *Week 0* | *Week 4* | *P* |
| Weekly nocturia | 12 87 | 10.46 | 14.92 | 16.10 | <0.01* |
| Volume voided (F/V chart) (ml) | 149.8 | 172.7 | 155.6 | 158.60 | <0.05* |
| Spontaneous peak flow rate (ml/min) | 7.13 | 8 94 | 5.80 | 5.6 | <0.05* |
| CMG peak flow rate (ml/min) | 6.71 | 9.36 | 7 00 | 6 56 | <0.01* |
| Residual urine (ml) | 103 5 | 49.1 | 97.0 | 97.0 | <0.05 |
| Urethral resistance (median) | 1.81 | 0.58 | 2.19 | 2.08 | >0.05 |
| Daily frequency | 8.06 | 7.28 | 8.50 | 8.38 | NS |
| Bladder volume at first unstable wave (ml) | 200.7 | 212.1 | 149.4 | 163.2 | NS |
| Detrusor pressure at peak flow (cm $H_2O$) | 97.8 | 81.2 | 106.9 | 103.4 | NS |

* Analysed after adjustment for differences between treatment groups at Week 0 using an analysis of covariance.

with placebo and were then assessed by history, frequency/volume chart, urine flow rate, urethral pressure profilometry (Brown and Wickham, 1969) and filling and voiding cystometry (Week 0). They were then randomised to receive either 20 mg indoramin twice daily or placebo. After 4 weeks, patients were reassessed as at week 0. The methods, definitions and units used are those proposed by the International Continence Society. The results were analysed using analysis of covariance, *t* test or Mann Whitney U test as appropriate.

## Results

Of the 40 patients, 34 (18 indoramin, 16 placebo) completed the trial; 5 withdrew because of side effects and 1 patient on indoramin was withdrawn because of poor compliance. Both groups were well matched at week 0 for all parameters with the exception of instability, only 28% of those on indoramin being stable, compared with 69% of those in the placebo group.

Statistically significant improvement was seen in nocturia, volume voided (F/V chart), spontaneous and CMG flow rates, residual urine and urethral resistance ($P/F^2$). Improvement, though not statistically significant, was also seen in frequency, the bladder volume at the first unstable wave and the detrusor pressure at peak flow (Table 1). Hesitancy and urgency were improved equally in both indoramin and placebo groups, and prostatic height was reduced equally in both groups. Other parameters remained unchanged.

Global assessment of response to treatment at the end of the trial suggested that 89% of patients on indoramin and 75% of those of placebo were improved ($\chi^2$, not significant). No patient deteriorated during the course of the trial.

Side effects were noted in 7 patients on indoramin and 7 on placebo (Table 2). In 1 patient on indoramin and 4 on placebo they were severe enough to warrant cessation of treatment.

## Discussion

This study shows that both symptoms and objective urodynamic parameters were improved by treatment with indoramin and suggests that it may be a useful agent in the treatment of prostatic bladder outflow obstruction.

Whilst residual urine and urethral resistance were considerably improved, other parameters were not greatly altered (although the changes achieved statistical significance when compared with those in the placebo group). In particular, the peak flow rate, which might be expected to be the most responsive parameter, did not increase enormously. Other double-blind studies of indoramin have shown greater improvements in flow rate (Iacavou and Dunn, 1987; Chow *et al.*, 1990), although Iacavou and Dunn observed no changes in other urodynamic parameters.

**Table 2** Numbers of Patients Experiencing Side Effects (figures in brackets indicate patients withdrawing because of side effects)

| | *Indoramin* | *Placebo* |
|---|---|---|
| Lassitude | 3 (1) | 4 (1) |
| Abdominal pain | 1 | 1 (1) |
| Nasal congestion | 2 | 0 |
| Postural hypotension | 1 | 0 |
| Blurred vision | 1 | 0 |
| Migraine | 0 | 1 (1) |
| Retention | 0 | 1 (1) |
| Troublesome erections | 0 | 1 |

Although both parameters improved on indoramin in this study, the mean peak flow rate remained low and the mean detrusor pressure during voiding remained high, suggesting that significant outflow obstruction persisted (although urethral resistance was reduced to 0.58). This is not surprising, since indoramin would be expected to reduce only the smooth muscle element of the obstruction, leaving the adenomatous (anatomical) element unaltered. Better results are generally obtained following prostatectomy, although even here up to 25% of patients continue to have urodynamically demonstrable obstruction post-operatively (Abrams *et al.*, 1979).

In the indoramin group the side effects were largely those associated with α-blocking agents, although postural hypotension was not a significant problem. The incidence of side effects was relatively high (35%) but was equal in both treatment and control groups, suggesting that indoramin is a well tolerated drug. In only 1 patient on indoramin were the symptoms severe enough to cause him to stop taking the drug.

Given the low morbidity and mortality of definitive surgical treatment of prostatic obstruction, the use of α-blocking agents will be largely confined to symptomatic patients in whom surgery is deferred because of long waiting lists or because of business or domestic commitments. However, they may also have a role in the treatment of patients whose symptoms are not severe enough to warrant surgery or as a therapeutic trial in patients with mixed instability/obstruction in whom operative results are less predictable. They may also have a prophylactic role in the prevention of peri-operative retention in patients with outflow obstruction undergoing other surgical procedures or in achieving successful voiding in patients after an episode of acute retention.

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# Comparison of LHRH Analogue (Zoladex) with Orchiectomy in Patients with Metastatic Prostatic Carcinoma

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Summary—Between November 1983 and February 1986, 358 patients with previously untreated metastatic prostatic carcinoma entered a multicentre, randomised trial in the United Kingdom and the Republic of Ireland, in which the LHRH analogue Zoladex (ICI Pharmaceuticals PLC), administered subcutaneously every 28 days, was compared with orchiectomy. Both treatments were equally effective in lowering serum testosterone concentrations to within the surgically castrate range and this was accompanied by equivalent subjective and objective response rates and times to treatment failure. At a median follow-up of 2 years there was no difference in overall survival, confirming that Zoladex is an effective medical alternative to orchiectomy in patients with metastatic disease.

In 1977, Auclair *et al.* reported that the daily administration of luteinising hormone-releasing hormone (LHRH) analogues to male patients caused a reduction in the concentrations of LH and testosterone in plasma. From this and other subsequent studies, evidence accumulated to indicate the potential of the LHRH analogues as a possible practical alternative to surgical orchiectomy for the treatment of advanced prostate cancer.

It was considered essential, however, before any conclusion could be drawn about their clinical value, that their therapeutic effects should be compared with those of surgical orchiectomy, regarded by many urologists as the yardstick for the treatment of advanced disease. Although orchiectomy provides palliation of the disease in 70 to 80% of patients, the procedure is not without drawbacks. It is irreversible and for the 20 to 30% of patients whose tumours are not hormone-dependent, it could be argued that the operation provides no benefit. In addition, most patients with prostate cancer are elderly and therefore less able to tolerate the trauma of general anaesthesia and surgery; in younger patients there may be psychological effects.

This controlled, randomised clinical study was therefore designed to compare the efficacy and safety of Zoladex (an LHRH analogue) with bilateral orchiectomy in the treatment of advanced prostate cancer.

## Patients and Methods

Seventeen centres in the United Kingdom and the Republic of Ireland participated in the study. Recruitment began in November 1983 and closed in February 1986. Patients were randomised to either Zoladex therapy or total or subcapsular orchiectomy. When the study began, Zoladex was available only as an aqueous daily injectable formulation containing 250 μg of the drug. On 1 October 1984, a depot formulation containing 3.6 mg of the drug dispersed in a matrix of d-1-lactide-glycolide ‘copolymer’ for subcutaneous administration every 28 days became available. All

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patients randomised to Zoladex, on or after that date, received the depot formulation and are referred to as "depot period" patients. Patients who were being treated with the daily injectable formulation subsequently received the depot formulation. At entry, all patients had histologically-proven metastatic cancer of the prostate with radiological and/or isotope evidence of bone metastases (or evidence of soft tissue metastases), a life expectancy of more than 3 months and were fit for orchiectomy. Patients who had previously received hormonal therapy or orchiectomy, and those with prior or concurrent malignancy except of the skin or lip excluding melanoma, were not eligible for entry into the study. Ethical committee approval was received from all centres and all patients gave informed consent prior to randomisation.

A separate randomisation scheme was produced for each centre. This grouped the patients in blocks so that in every block there was the same number of patients in each treatment arm. Patients who refused the allocated treatment were offered orchiectomy if Zoladex had been allocated and second-line conventional treatment if orchiectomy had been allocated. None of the latter patients received Zoladex. These patients were included in analyses of response and survival according to the randomly allocated treatment.

Patients were retained in the assigned groups until withdrawal from the study for any of the following reasons: progression of disease, severe adverse reaction to Zoladex therapy, patient unwilling or unable to continue to receive Zoladex or unable to come to the hospital for assessment, or death.

When the patient was withdrawn from the study because of disease progression, secondary treatment was the responsibility of the investigator at each centre. Further follow-up of all patients was continued to determine survival and the cause of death.

Patients were assessed before treatment, at 4-weekly intervals for the first 3 months and at 12-weekly intervals thereafter. They were evaluated for response (subjective and objective), physiological effects of testosterone withdrawal (hot flushes, breast swelling, breast tenderness, decrease in libido and erections) and safety. Serum LH and testosterone were determined together with routine haematological (red blood cell count, white blood cell count, platelet count, haemoglobin, haematocrit and erythrocyte sedimentation rate or plasma viscosity) and biochemical indices (serum urea, creatinine, total bilirubin, alkaline phosphatase, albumin, total protein, alanine transaminase, aspartate transaminase, gamma glutamyl transferase, calcium and inorganic phosphate).

Subjective and objective responses to treatment were assessed in patients randomised to therapy on or after 1 October 1984, the "depot period" patients. Subjective response was based on improvement in urological symptoms, performance status, decrease in bone pain and/or analgesic requirement and was assessed both by a scoring system stipulated in the protocol and according to the clinicians' opinion. Objective response was assessed according to the British Prostate Group Criteria (Chisholm, 1980) with the following modifications:

(i) Where patients underwent a transurethral resection of the prostate following randomisation or during the follow-up period, they were not evaluable for the assessment of objective response to therapy at that site.

(ii) Where patients had received radiotherapy to the primary tumour or to a metastatic site during the follow-up period, these sites were only assessable for objective response to therapy up to the time of radiotherapy.

Only eligible patients randomised on or after 1 October 1984 were used in the analyses of subjective, objective and endocrine responses. All patients were evaluated for survival. Analyses were performed according to the treatment to which the patient was randomly allocated, irrespective of whether or not this treatment was actually received. In the analyses of the physiological effects of testosterone withdrawal and of safety and laboratory variables, patients were categorised according to treatment actually received.

## Statistical Methodology

Demographic data for eligible patients in each treatment group were compared. Differences between the groups in mean age and mean weight were tested for statistical significance using Student's *t* test. The chi-squared test was used to determine if there were any significant differences in the distributions of histological grades and T category of the primary tumour.

Subjective response rates according to the protocol criteria were compared between the 2 treatment groups using the chi-squared test. The median times from the date of orchiectomy or first Zoladex injection to the date of first subjective response were calculated by the life table method of Kaplan and Meier (1958) and distributions of times to subjective response were compared using the logrank test. The statistical significance of the difference in the clinicians' assessment of subjective response between the 2 groups of patients was assessed using Fisher's exact test.

For each patient who met the inclusion criteria for the study there were 3 measures of objective response to treatment:

(i) The overall response was defined as the best response which occurred up to and including the first objective assessment of disease progression and withdrawal from the study. Differences in response rates between the 2 treatment groups were compared using the chi-squared test.

(ii) The time to response was defined as the time from the date of the start of treatment to the date of the first documentation of complete or partial response.

(iii) The time to treatment failure was defined as the time from the date of the start of treatment to the date of treatment failure or withdrawal from the study. The duration of response was also analysed separately for patients who had an objective response (complete and partial) to treatment.

Mean time to response and median time to treatment failure were calculated by the life table method of Kaplan and Meier (1958) and compared using logrank tests (Peto *et al.*, 1976, 1977).

The survival time for patients was determined from the date of randomisation to the date of death or, if death had not occurred, to the date last known to be alive. Survival curves were again calculated using the life table method of Kaplan and Meier (1958) and the logrank test (Peto *et al.*, 1976, 1977).

In the analysis of endocrine and laboratory variables, the statistical significance of the differences between the 2 treatment groups was assessed using Student's *t* test. The proportions of patients in the 2 groups showing physiological effects due to testosterone withdrawal (*i.e.* breast swelling and tenderness, suppression of libido and erections, when present before treatment, and the appearance of hot flushes) were compared using the chi-squared test or squared Fisher's exact test.

**Table 1** Entry Characteristics for Eligible "Depot Period" Patients

| | *Randomised treatment* | | |
|---|---|---|---|
| | *Zoladex* | *Orchiectomy* | *Statistical significance* |
| No. of patients satisfying inclusion criteria | 148 | 144 | |
| Mean age in years | 71.8 | 72.5 | N.S.* |
| (range) | (49–86) | (55.89) | |
| Mean weight in kg | 69.6 | 70.5 | N.S.* |
| (range) | (36–95.7) | (44.6–110) | |
| Histological grade | | | |
| G1 (high degree) | 20 | 28 | N.S.† |
| G2 (medium degree) | 62 | 54 | |
| G3 (low degree) | 50 | 46 | |
| GX (not assessed) | 14 | 15 | |
| T category | | | |
| Not known | 2 | 3 | N.S.† |
| T0 (no tumour palpable) | 3 | 2 | |
| T1 (intracapsular) | 7 | 8 | |
| T2 (intracapsular, nodular deforming contour) | 28 | 38 | |
| T3 (extracapsular spread) | 62 | 51 | |
| T4 (fixed) | 43 | 42 | |
| TX (not assessed) | 3 | 0 | |

N S. = not statistically significant; * = Student's *t* test; † = Chi-squared test.

## Results

A total of 358 patients entered the study. Fourteen patients randomised to receive Zoladex and 19 randomised to orchiectomy did not satisfy the inclusion criteria. In the Zoladex group, 4 patients had non-metastatic disease, 1 had no histological confirmation of prostatic cancer, 4 had received prior hormone therapy and 5 had prior or concurrent malignant disease. In the orchiectomy group, 5 patients had non-metastatic disease, 7 had no histological confirmation of prostatic cancer, 2 had received prior hormone therapy and 5 patients had prior or concurrent malignant disease. Of the remaining patients who fulfilled the entry criteria, 292 entered the study on or after 1 October 1984; 148 were allocated to receive Zoladex and 144 underwent orchiectomy. Entry characteristics for these patients are presented in Table 1, from which it can be seen that there were no statistically significant differences in any of these parameters between the treatment groups.

The mean duration of on-study follow-up has been 65.8 weeks in the Zoladex group and 59.6 weeks in those who underwent orchiectomy. The median duration of follow-up for survival in the Zoladex and orchiectomy groups has been 104 weeks and 97 weeks respectively.

Of the patients symptomatic at entry, 66% (41/62) randomised to Zoladex and 73% (43/57) randomised to orchiectomy had a favourable subjective response to therapy by the protocol criteria and 94% (58/62) randomised to Zoladex and 95% (54/57) randomised to orchiectomy had a favourable response as assessed by the investigators.

The median times to the onset of a favourable subjective response by the protocol criteria, and by the investigators' own assessment, were 8 weeks and 5 weeks respectively in the Zoladex group and 9 weeks and 5 weeks in the orchiectomy group.

There were no statistically significant differences between the treatment groups in subjective response rates by both the protocol criteria ($P=0.36$) or by the investigators' own assessment ($P=1.0$). Similarly, there were no statistically significant differences in times taken to achieve a subjective response by both the protocol criteria ($P=0.74$) and clinicians' assessment ($P=0.77$).

Objective responses to therapy are shown in Table 2. There were no statistically significant differences between the treatment groups in any of the objective response data.

The survival experience of "depot period" patients and of all patients randomised into the study (irrespective of whether or not they fulfilled the inclusion criteria) are presented in Table 3 and displayed as life table survival curves in Figures 1 and 2. Although there were fewer deaths in the Zoladex group and the median survival times for patients in this group were greater than for the orchiectomy group, these differences were not statistically significant.

There were no differences in causes of death between the treatment groups; 58 patients in the

**Table 2** Objective Response Rates, Median Duration of Response and Time to Response

| | *Treatment group* | | |
|---|---|---|---|
| | *Zoladex ($n=148$)* | *Orchiectomy ($n=144$)* | *Statistical significance* |
| Response (%) | | | |
| Complete and partial | 71 | 72 | 0.91* |
| No change | 18 | 22 | |
| Disease progression | 11 | 6 | |
| Mean Time to Response (weeks) | 9.0 | 10.2 | 0.51† |
| Median Duration of response in responding patients (weeks) | 53.7 | 50.1 | 50.1‡ |
| Median time to treatment failure in all patients (weeks) | 26.9 | 40.3 | 40.3§ |

* Chi-squared test, † Student's $t$ test; ‡ Logrank test; § Cox analysis

**Table 3** Overall Survival of Patients

| | *Randomised treatment* | | *Statistical significance* |
|---|---|---|---|
| | *Zoladex* | *Orchiectomy* | |
| "Depot Period" patients | | | |
| No. of patients | 148 | 144 | |
| No. of deaths | 84 | 89 | $P=0.33$* |
| Median survival (weeks) | 115 | 104 | |
| All patients | | | |
| No. of patients | 176 | 182 | |
| No. of deaths | 102 | 116 | $P=0.23$* |
| Median survival (weeks) | 110 | 99 | |

* = Logrank test.

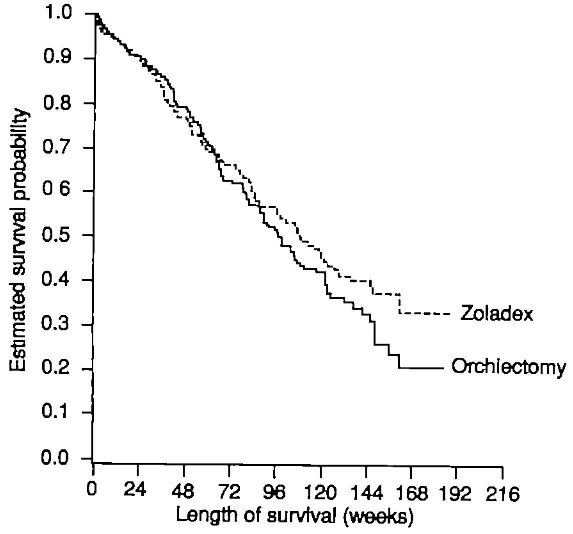

**Fig. 1** Survival (all patients).

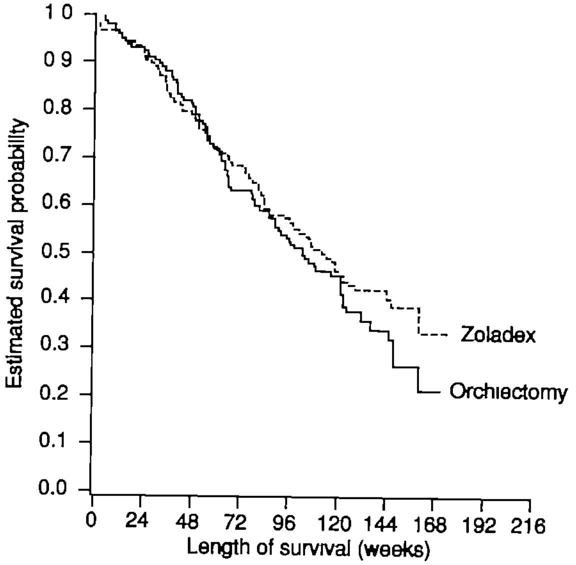

**Fig. 2** Survival ("Depot Period" patients only).

**Table 4** Physiological Effects of Zoladex and Orchiectomy

| | *Zoladex* | | | *Orchiectomy* | | | |
|---|---|---|---|---|---|---|---|
| | *No of patients assessed* | *No. of patients with effect* | *(%)* | *No. of patients assessed* | *No. of patients with effect* | *(%)* | *Statistical significance* |
| Decrease in libido* | 51 | 37 | (73) | 43 | 34 | (79) | NS |
| Decrease in erections* | 51 | 43 | (84) | 48 | 41 | (85) | NS |
| Hot flushs† | 152 | 96 | (63) | 163 | 94 | (58) | NS |
| Breast swelling† | 168 | 8 | (4.8) | 173 | 7 | (4.0) | NS |
| Breast tenderness† | 167 | 1 | (0.6) | 173 | 2 | (1.2) | NS |

* = Present at entry.
† = Absent at entry.
NS = Not statistically significant.

Zoladex group and 61 in the orchiectomy group died of disseminated prostate cancer; 35 Zoladex-treated patients and 37 patients who received an orchiectomy died of disseminated prostate cancer and other causes. In 8 of the Zoladex group and 16 of the orchiectomy group, death was not due to prostate cancer; in 1 Zoladex-treated patient and 2 patients who received orchiectomy the cause of death was unknown.

In the Zoladex group, mean serum testosterone decreased from a mean pre-treatment value of 12.46 nmol/l to 1.26 nmol/l after 4 weeks of therapy and remained suppressed for the duration of treatment. In patients who underwent orchiectomy, mean serum testosterone decreased from a pre-treatment value of 11.09 nmol/l to 0.91 nmol/l by week 4.

In the Zoladex group, mean serum LH decreased from a mean pre-treatment value of 8.58 iu/l to 1.47 iu/l by week 4 and thereafter remained suppressed. In contrast, but as expected, in the group which underwent orchiectomy, LH rose from a mean pre-treatment value of 6.69 iu/l to 20.8 iu/l at week 4 and remained elevated.

The physiological effects of testosterone withdrawal are shown in Table 4. No differences were seen in the incidence of these effects between the treatment groups.

An analysis of laboratory variables showed no consistent changes in any of the indices throughout the course of the study.

Possible adverse reactions to treatment are summarised in Table 5. It can be seen that Zoladex was well tolerated; indeed, no patient was withdrawn from the study due to side effects of treatment. Six patients receiving Zoladex reported a transient increase in bone pain within the first few weeks of therapy. This was managed by increasing the use of analgesics during that time. In contrast, 14 patients who underwent orchiectomy developed post-operative complications, usually scrotal abscesses and haematomas. One patient in the orchiectomy group suffered a respiratory arrest following surgery and required ventilation. One patient in each treatment group developed paraplegia following initiation of therapy. There were no reports of ureteric obstruction in either group. Other possible adverse reactions occurring in both groups were mild and transient.

**Table 5** Summary of Possible Adverse Reactions

| | *Zoladex* | *Orchiectomy* |
|---|---|---|
| Transient increase in pain in the first 4 weeks | 6 | 0 |
| Problems at initiation of therapy (*i.e.* post-operative complications) | 0 | 14 |
| Central nervous system (taste disturbance, dizziness, visual disturbance) | 4 | 0 |
| Respiratory system (breathlessness) | 0 | 1 |
| Musculoskeletal system (polyarthralgia) | 1 | 0 |
| Skin (skin rash, urticaria) | 5 | 0 |
| Oedema (mild) | 1 | 0 |
| Cardiovascular system (cardiovascular accident, deep vein thrombosis) | 2 | 0 |
| Digestive system (diarrhoea, nausea, gingival atrophy, pain) | 6 | 0 |

## Discussion

From a clinician's viewpoint, if LHRH analogues are to challenge the place of orchiectomy as the generally accepted first-line treatment for advanced prostate cancer, their use must be shown to be:

(1) Equivalent to orchiectomy in the suppression of the concentration of serum testosterone to the surgically castrate level.
(2) As effective as orchiectomy in the relief of symptoms, especially bone pain.
(3) As effective as orchiectomy in influencing the overall rate and duration of objective response with equivalent survival.

In addition, they should be acceptable to the patients as a form of treatment.

This study showed that the mean concentration of serum testosterone was the same after Zoladex as after orchiectomy and was maintained at the "castrate level" for the duration of treatment.

Nevertheless, in detail such endocrinological response was not exactly similar to that which follows orchiectomy, for the initial surge of plasma testosterone that is well known during the first week of treatment with LHRH analogues, and which does not occur with orchiectomy, was not evident in this trial because of the terms of the protocol. It would, however, be unrealistic to over-emphasise this phenomenon because a "flare response" in this trial was reported in only 6 of 161 patients (under 2%), and those with an exacerbation of pain at the beginning of the treatment were easily managed by a temporary increased use of analgesics. Nevertheless, "flare response" cannot be dismissed lightly in patients with incipient spinal compression from metastases, or those with impending ureteric obstruction, although these complications were rare in this trial.

In this study, there was no significant difference in the overall subjective response rates or the individual symptomatic response rates in either treatment arm. In particular, Zoladex was as effective as orchiectomy in achieving relief of bone pain.

The overall best objective responses in this trial were not significantly different in either treatment arm. Similarly, deaths from prostatic cancer, median survival times and overall survival rates were not significantly different regardless of whether the patients had been treated with Zoladex or by orchiectomy.

No serious adverse reactions to Zoladex were noted and no local reactions at the site of injection were recorded. In contrast, scrotal infections and other local problems were recorded at the operation site in 14 patients who underwent orchiectomy.

One point at issue concerns the willingness of patients to submit to the monthly inconvenience of undergoing an injection, despite the fact that it is an easy and quick procedure and not uncomfortable. There were 10 withdrawals from the Zoladex arm of the trial which were not related to the cancer process; of these only 1 patient requested discontinuation of the drug and another 2 were lost to follow-up, so that the patients' compliance with Zoladex was almost complete. There was, of course, total compliance with orchiectomy.

Symptoms resulting from androgen withdrawal, such as hot flushes, loss of libido and reduction of sexual potency, are accepted as part of the price of treatment by orchiectomy. In this trial, similar symptoms occurred in patients treated with Zoladex and there was no significant difference in pattern from those treated by orchiectomy.

The conclusions from this phase III trial that compared the effectiveness of treatment of men with metastatic (M1) prostate cancer by administration of the depot formulation of Zoladex against orchiectomy are:

(1) That the groups formed by random allocation of treatment were comparable in characteristics at entry.
(2) That repeated subcutaneous administration every 28 days of 3.6 mg of the depot formulation of Zoladex was as effective as orchiectomy in lowering serum testosterone and maintaining it at castrate levels.
(3) Subjective and objective response rates were similar.
(4) Duration of response and time to treatment failure were similar.
(5) Survival rates were similar.

This trial, therefore, demonstrated that the depot formulation of Zoladex is a medical alternative to surgical orchiectomy for the management of patients with metastatic prostate cancer.

## Acknowledgements

The authors thank ICI Pharmaceuticals PLC for their support and for the provision of Zoladex. In addition, we appreciate the invaluable assistance of Dr A. Turkes of the Tenovus Institute for Cancer Research, Cardiff, and of all participants in the trial, listed below, without whose efforts this study would have been impossible. J. G. Roberts (Bangor), A. G. Evans (Bridgend), P. J. B. Smith, and J. B. M. Roberts (Royal Infirmary, Bristol), R. W. M Rees (Cardiff), M. R. Heal (Crewe), J A Heaney (Dublin), D G. Calvert (Gloucester), Professor N. J Blacklock and C. Buck (Manchester), R. H. P. Williams (Neath), J. C. Smith and G J. Fellows (Oxford), J. C. Hammonds and W. Gall (Plymouth), A. L. Hart (Pontypridd), J. C. Gingell (Southmead Hospital, Bristol), M. B. Rose and K. C. Vaughton (Swansea), P. G. O'Boyle (Taunton).

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# Fractures of the Penis: Therapeutic Approach and Long-term Results

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Summary—Injury to the external male genitalia is considered, with attention focused on accidental fracture of the corpora cavernosa (by coitus or masturbation). Such injuries are often complicated by urethral lesions. We present 13 patients with either simple or complicated fracture of the penis, all of whom were operated on between 2 h and 8 days following injury, with excellent functional results. The need for immediate surgery is emphasised, in order to avoid erectile failure and curvature, which are typical complications of conservative treatment. Surgery consists of complete evacuation of haematoma, curettage and repair of the albuginea. If the fracture is associated with urethral disruption, the latter is also repaired.

Injuries to the penis, including fracture of the corpora cavernosa, are not always reported (Redman and Miedema, 1981). The injury consists of rupture of the tunica albuginea of one or both corpora cavernosa, with possible involvement of the corpus spongiosum and the urethra. The effusion of blood, urine or both may extend to the scrotum, the perineum and the inguinal region (Al Saleh *et al.*, 1985).

Fractures of the corpora cavernosa usually occur during coitus ("faux pas de coit", "texas trauma", or "bent nail syndrome") (Gross *et al.*, 1977), during masturbation or nocturnal unconscious manipulation. A sudden "whip crack", violent pain, rapid flaccidity and deformity of the penis, followed by haematoma, are typical symptoms.

## Patients and Methods

Over an 8-year period (1982–1989) we observed 38 cases of open and closed genital trauma, of which 23 were testicular and 15 penile (2 external injuries and 13 fractures). Fractures of the penis are listed in the Table. Operation was always preceded by a careful examination to ascertain site, extent and type of lesion. In the case of urethral haemorrhage, retrograde urethrography was performed. The number of penile injuries was high, but Treviso Hospital serves a population of 300,000 to 400,000. In most cases a circumferential coronal incision below the glans was used, in order to expose both corpora cavernosa and the urethra as much as possible, particularly for complex lesions or in cases of difficult diagnosis. A longitudinal penile incision was used for single, small lesions with limited haematomas and oedema and for fractures of the corpora cavernosa at the root of the penis.

The operation comprised complete evacuation of the haematoma, curettage of the area involved and repair of the albugineal gap with possible repair of the urethra. Defects in the tunica albuginea were repaired with 4/0 Dexon interrupted sutures. In 3 patients (cases 3, 10 and 13), the trauma was associated with complete disruption of the urethra; we performed a partial urethrectomy and immediate urethroplasty with absorbable sutures (3/0 or 4/0 chromic catgut) supported by a urethral stent and defunctionalised by suprapubic cystostomy.

Operations were performed within 2 h to 8 days following injury. Ten patients were treated within the first 8 h and 2 (cases 4 and 8), for whom treatment was delayed, presented with a residual fibrous spot in association with slight deviation of the penis during erection which still, however,

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**Table** Penile Fractures

| *Case No.* | *Age (years)* | *Cause* | *Type of Lesion* | *Operation* | *Time from trauma* | *Results* |
|---|---|---|---|---|---|---|
| (1) | M M 23 | Sexual manoeuvres | R.c. cavernosum fracture | Suture of albuginea | 6 h | Good |
| (2) | M G 32 | Sexual manoeuvres | R c. cavernosum fracture | Curettage of haematoma.<br>Suture of albuginea | 8 days | Good |
| (3) | S.L. 36 | Sexual manoeuvres | Bilateral c. cavernosa fracture and urethral lesion | Suture of albuginea.<br>Urethrectomy followed by urethroplasty | 4 h | Good |
| (4) | O F 44 | Unconscious nocturnal manipulation | R.c. cavernosum fracture | Curettage of haematoma.<br>Suture of albuginea | 2 days | Fibrous spot.<br>Slight bend.<br>Coitus possible |
| (5) | Z.A 51 | Sexual manoeuvres | R.c. cavernosum rupture | Suture of albuginea | 8 h | Good |
| (6) | S.T. 34 | Sexual manoeuvres | L c. cavernosum rupture | Suture of albuginea | 3 h | Good |
| (7) | B.A. 43 | Sexual manoeuvres | L.c cavernosum rupture | Suture of albuginea | 2 h | Fibrous spot.<br>No problems. |
| (8) | C.G 38 | Sexual manoeuvres | R.c. cavernosum rupture | Curettage of haematoma.<br>Suture of albuginea | 2 days | Fibrous spot.<br>Coitus possible |
| (9) | F.C 40 | Sexual manoeuvres | Bilateral c. cavernosa rupture | Curettage of haematoma.<br>Suture of albuginea | 4 h | Good |
| (10) | B.Y. 43 | Sexual manoeuvres | Bilateral c. cavernosa rupture and urethral lesion | Curettage of haematoma.<br>Suture of albuginea and urethroplasty | 16 h | Good |
| (11) | C.A. 40 | Sexual manoeuvres | L.c. cavernosum root rupture | Curettage of haematoma.<br>Suture of albuginea | 6 h | Good |
| (12) | F.M. 42 | Sexual manoeuvres | L.c. cavernosum rupture | Curettage of haematoma.<br>Suture of albuginea | 4 h | Good |
| (13) | P R. 41 | Sexual manoeuvres | Bilateral c. cavernosa rupture and urethral lesion | Curettage of haematoma.<br>Suture of albuginea and urethroplasty | 12 h | Good |

allowed regular coitus. Late or postponed operation gave less favourable results owing to sepsis or urinary infiltration, and necessitated a deeper curettage, the cutting of newly formed fibrous tissue and the removal of the intraspongeous fibrotic wedge (Anselmo *et al.*, 1983).

## Results

There were no post-operative complications and patients were discharged on the fourth day after operation except for those with urethral injury, who remained in hospital for 12 days. Follow-up ranged from 6 months to 8 years. Ten patients had a normal penis on erection with excellent functional results; 3 had mild curvature but normal erectile potency and regular coitus. Uroflowmetry and urethrography were normal in all 3 patients with repaired urethral disruption. The only patient who, for reasons beyond our control, underwent operation 8 days after trauma, had very good results.

## Discussion

There is some controversy about the approach to traumatic ruptures of the penis and many support the necessity for immediate surgery (Anselmo *et al.*, 1983; Kalash and Young, 1984). The aim of immediate restoration of anatomical continuity in the albuginea is to avoid the formation of fibrous tissue, which causes bending of the penis towards the affected side in unilateral fractures, and upwards or downwards in bilateral or complex ones. In lesions that are diagnosed soon after injury the haematoma is limited; in more serious lesions, or following late diagnosis, the haematoma spreads to the scrotum, perineum, groin and hypogastrium. Typical too is the "gap" in the albuginea. Retrograde urethrography should always be performed when urethral lesions are suspected, while cavernography helps, in doubtful or complex cases, to define the site, extent and seriousness of the lesion. A simple vertical lancing may be sufficient in recent simple lesions with limited haematoma and oedema, but it is usually advisable to perform a circumferential coronal incision under the glans in order to expose both the corpus cavernosum and repair any gaps in the albuginea, which might be wider and more irregular than supposed during observation before surgery.

We feel that immediate surgical exploration avoids the formation of fibrous tissue, chordee, painful or partial erections, or urethral stenoses (Pryor *et al.*, 1981; Bergner *et al.*, 1982; Ozen *et al.*, 1986). Prompt surgery allows an earlier resumption of sexual activity with less likelihood of the psychophysical, social or medico-legal problems which are typical of this kind of pathology, especially in the young.

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# Non-invasive Assessment of Arteriogenic Impotence: A Comparative Study

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Summary—This study was undertaken to determine the relative accuracy of computerised Doppler waveform analysis and colour coded duplex ultrasonography in the diagnosis of arteriogenic impotence. Twenty men with ostensibly normal penile haemodynamics were compared with 50 men whose impotence was considered due to compromised penile haemodynamics. In each patient the penile arterial inflow was assessed by both methods of investigation, which were performed at an interval of 2 weeks. The results demonstrated both techniques to be sensitive in detecting penile artery insufficiency but colour coded duplex ultrasonography was significantly more accurate.

The use of computerised Doppler waveform analysis (CDWA) for the assessment of penile artery flow was originally reported by Desai *et al.* (1987) and has become part of our standard protocol for the investigation of impotent men who have failed to respond to intracavernosal papaverine (ICP). Duplex ultrasonography (DDU) with colour imaging is a relatively recent innovation which is increasingly being used in the diagnosis of vascular disease, including impotence. We wished to establish whether DDU offered any advantages over our present practice in differentiating normal from abnormal penile artery function and we present the results of a study comparing the 2 techniques.

## Patients and Methods

Each patient underwent preliminary evaluation by history, examination and ICP test. Those with neither risk factors for nor signs of arterial disease and who responded fully to ICP, *i.e.* with a fully rigid erection lasting for longer than 20 min, were considered to have normal penile haemodynamics. They were ascribed to group A ($n=20$). Those who failed to respond to papaverine (maximum dose 60 mg) with an erection adequate for penetration, and who also had evidence of coexistent arterial disease, were ascribed to group B ($n=50$). Each patient underwent assessment of penile artery flow by means of DDU and CDWA. Both investigations were performed by the same investigator (H.W.G.) at an interval of at least 2 weeks.

The DDU study was carried out using equipment incorporating a colour mapping facility (Acuson-128, Acuson Corporation). With the patient lying supine, the flaccid penis was placed in the anatomical position and scanned with a 7 MHz linear array probe. Areas of calcification or Peyronie's plaques were noted and the internal diameters of the cavernosal arteries were determined. A tourniquet was placed around the base of the penis and 60 mg of papaverine were injected, with a 25 SWG needle, into the right corpus cavernosum; the patient massaged the penis to ensure complete distribution. The tourniquet was released after 2 min. With the penis lying in the inguinal groove and the transducer placed longitudinally along its ventrolateral surface, the right cavernosal artery was identified and, having corrected for the Doppler angle, the blood flow was monitored. When the maximal response was observed, characterised by maximal systolic and diastolic flow velocities, the peak flow velocity was recorded. The left artery was then immediately imaged and its peak flow velocity recorded. The

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internal calibre of both vessels was measured again, always at the systolic peak in order to ensure uniformity. The patient was then allowed to return home but was given written instructions to return should an erection develop which persisted for more than 6 h.

Two weeks later each patient underwent computerised Doppler waveform analysis according to the method described by Desai *et al.* (1987).

Only the cavernosal arteries were assessed during both investigations because evaluation of the dorsal arteries, in view of their minor contribution to erection, was considered unnecessary (Lue *et al.*, 1985a).

## Results

### *Group A (n=20)*

The mean age of these patients was 52 years (range 34–62). The mean duration of impotence at the time of presentation was 37 months (range 6–120). All responded to ICP (maximum 60 mg) with a full erection lasting at least 20 min. The aetiology of the impotence was neuropathic in 3 cases (2 with spinal injury, 1 with multiple sclerosis). In the remainder the aetiology was psychogenic.

### *Group B (n=50)*

All patients in this group had evidence of arterial disease (Table 1) and had failed to respond to 60 mg of ICP on at least 2 occasions. Their mean age was 60 years (range 45–74). The mean duration of impotence at the time of presentation was 49 months (range 6–180).

The results of DDS and CDWA are given in Table 2. No episodes of prolonged erection occurred during the course of the study.

### *Statistical analysis*

The sensitivity and specificity of these tests, in the absence of an acceptable 'gold standard', cannot be determined. The data obtained were, therefore, analysed to determine the relative ability of each test to differentiate the 2 groups.

The mean values of peak flow velocity (DDU), percentage internal diameter increase (DDU) and damping factor (CDWA) were calculated in each case. The 95% confidence interval was derived for each parameter from the data obtained from Group A. Using these figures as cut-off values, the relative accuracy of each parameter in differentiating the experimental groups was determined (Table 2).

Patients who were subsequently shown to have venous leakage (*vide infra*) and to have either a mean peak flow velocity, an internal calibre increment or a damping factor above the cut-off value were excluded from this analysis. On this basis, the accuracy of the mean peak flow velocity as measured by DDU was significantly greater than that of the mean damping factor obtained from CDWA ($\chi^2=3.90$, $P<0.05$, 1 df).

**Table 1** Evidence of Arterial Disease in Group B

| | *No.* | *(%)* |
|---|---|---|
| Hypertension | 15 | 30 |
| Ischaemic heart disease | 12 | 24 |
| Peripheral vascular disease. | | |
| Aorto/iliac/femoral | 18 | 36 |
| Cerebral | 3 | 6 |
| Diabetes mellitus | 9 | 18 |
| Cigarette smoking (>10/day >10 years) | 23 | 46 |

### *Venous leakage*

Six men who had failed to respond to ICP were nevertheless found to have peak flow velocities above the established cut-off value (28 cm/s). All underwent pharmacocavernosometry; in 5 cases (83%), venous leakage was demonstrated using criteria established by Desai (1988). The aetiology of the sixth patient's impotence remains unclear; it is possible that psychogenic inhibition resulted in spurious observations.

## Discussion

The accurate measurement of penile artery function is essential when seeking to restore potency by means of either cavernosal revascularisation or venous ligation (Lewis, 1990). Selective internal iliac arteriography, when performed with the aid of simultaneous intracavernosal injection of papaverine and penile magnification, can provide excellent anatomical definition of the arterial supply to the penis (Bookstein *et al.*, 1987; Bahren *et al.*, 1988). However, because of its invasive nature and its inability to yield functional information, it is not an appropriate screening test. It should be reserved for the immediate pre-operative investigation of men about to undergo penile revascularisation, in order to identify the precise site of arterial occlusion (Zorgniotti and Lizza, 1988).

Whilst it is generally accepted that a rigid erection occurring within a few minutes of an intracavernosal injection of papaverine indicates normal penile haemodynamics (Virag *et al.*, 1984),

**Table 2** Results

| | *Group A* | *Group B* | *Cut-off* | *Accuracy (%)* |
|---|---|---|---|---|
| Mean peak flow velocity (cm/s) | 48.3 (12.5) | 18.5 (6.2) | 28 | 95 |
| Internal diameter increment (%) | 172.3 (51.2) | 84.2 (57.8) | 88 | 72 |
| Damping factor | 0.46 (0.09) | 0.72 (0.11) | 0 61 | 86 |

Mean values (1 SD).

failure to respond does not necessarily imply a vascular abnormality (Buvat *et al.*, 1986). Furthermore, an equivocal response does not help in differentiating between impotence due to arterial insufficiency and that due to veno-occlusive incompetence. Nevertheless, the ability of papaverine to enhance cavernosal blood flow has been used to develop more sensitive tests of penile artery function which take into account the haemodynamic changes known to occur during erection.

CDWA, one such test, involves computerised analysis of dorsal and cavernosal artery waveforms recorded during pharmacologically induced tumescence with a 10 MHz continuous wave Doppler probe. The analysis is based upon a 3-pole mathematical model (the Laplace Transform) whose coefficients are related to proximal lumen size, vessel elasticity and peripheral resistance. We have found the coefficient (known as the damping factor) relating to the cavernosal artery waveforms recorded in early tumescence to be the parameter best able to discriminate between normal and abnormal penile arterial inflow (Desai, 1988).

Although this method can identify men with unequivocal arteriogenic impotence, it has drawbacks inherent in the use of a continuous wave Doppler probe. Identification of the cavernosal arteries is not always achieved and because the amplitude of the waveform is influenced by the angle of the incident ultrasound beam, the results may vary according to the experience of the operator.

These potential sources of error can, theoretically, be eliminated by employing duplex Doppler ultrasonography, which combines real time imaging with manoeuvrable range-gated pulsed Doppler spectral analysis. This technique was first applied to the investigation of penile artery function by Lue *et al.* (1985b), who proposed the use of cavernosal peak flow velocity as well as the increase in size of the cavernosal arteries during tumescence as discriminatory indices. DDU can be a difficult technique, however, requiring considerable operator skill not only to localise the cavernosal arteries but also to stabilise the sample volume and adjust the Doppler angle in order to measure peak flow velocity (Collins and Lewandowski, 1987; Shabsigh *et al.*, 1989). The advent of colour imaging, which represents blood flow in colours dependent upon its direction and velocity, has been a significant advance. A major advantage is that the cavernosal arteries can be identified almost as soon as scanning commences (Fig. 1), the importance of which becomes apparent when one considers the haemodynamics of erection.

The events that initiate erection are cavernosal sinusoid relaxation and arteriolar dilatation, both of which are caused by smooth muscle relaxation (Lue *et al.*, 1983). This results in a profound decrease in the peripheral resistance with a consequent surge in the cavernosal artery flow during both phases of the cardiac cycle. As erection proceeds, the rising intracavernosal pressure causes venous occlusion, which raises the pressure even further (Juenemann *et al.*, 1986). This reduces diastolic, and subsequently systolic, flow. These events are reflected in the characteristic changes in the cavernosal artery waveforms documented by Desai *et al.* (1987) during pharmacologically-induced erection. Maximum arterial flow occurs in early tumescence and it is this phase of erection, which begins approximately 2 min. after ICP, that represents the optimal time for assessment of cavernosal artery function (Schwartz *et al.*, 1989).

Because of the physiological rise in peripheral resistance that accompanies increasing erectile rigidity, delays in imaging the appropriate arteries may result in erroneously low measurement of peak flow velocities. The timing of measurement is, therefore, critical and readily met with the colour mapping facility which allows the cavernosal arteries to be identified within 30 s of the commencement of scanning. Also, by demonstrating the direction of the blood flow, colour DDU enables more precise alignment of the Doppler angle correction cursor, a further aid in circumstances where only a short segment of the often tortuous arteries is discernible (Fig. 2).

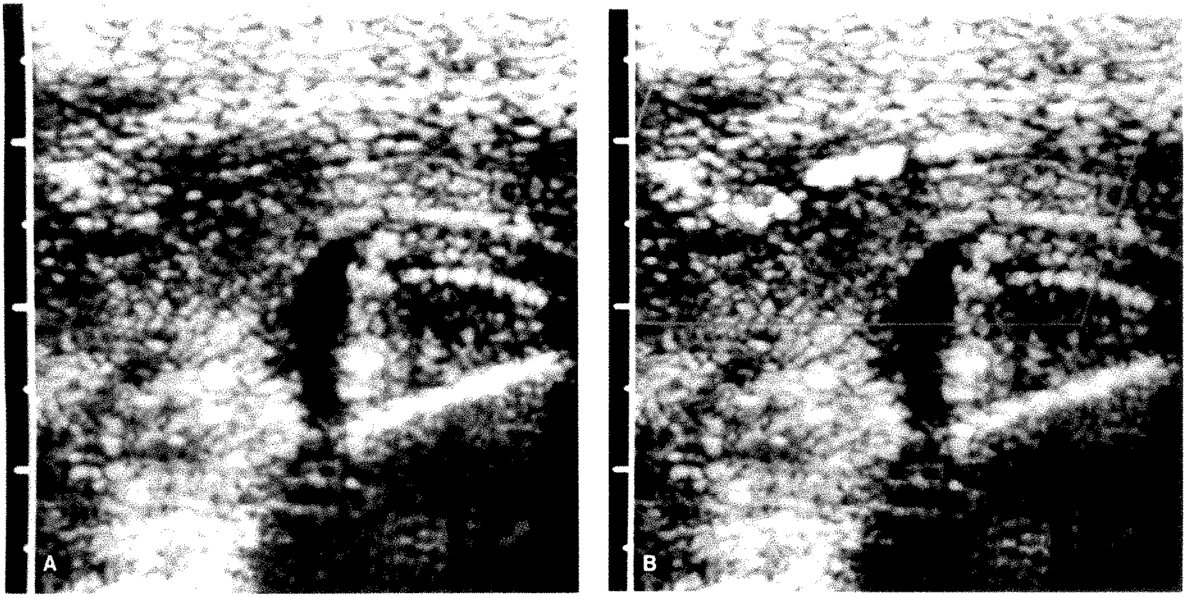

**Fig. 1** (A) Transverse real time image without colour imaging: the cavernosal artery is indistinguishable from other longitudinal structures. (B) With colour imaging the location of the cavernosal artery becomes obvious.

It is therefore not surprising that colour DDU has proved superior to CDWA in assessing arteriogenic impotence. Nevertheless, controversy remains regarding the precise parameters which should be measured, when using DDU, in order to discriminate between normal and abnormal penile artery function. Cavernosal peak flow velocity has been the most widely used discriminant, but there is no uniform agreement as to the exact cut-off value. Mueller and Lue (1988) and Quam *et al.* (1989) recommended a value of 25 cm/s. Our findings are similar, although we found a cut-off value of 28 cm/s to be more accurate. Benson and Vickers (1989) set a much higher limit of 40 cm/s above which arterial function can be considered normal. They defined severe arteriopathy on the basis of a cavernosal peak flow velocity <30 cm/s. Men with peak flow velocities of 30 to 40 cm/s were found to be in a group with mild to moderate disease. This group included men whose impotence was being successfully managed with intracavernosal vasoactive agents. It is possible that such men may have been included in our haemodynamically normal group. These apparently conflicting data, whilst partly attributable to differences in methodology, also reflect the difficulty in determining the value of any investigative technique in a field where no acceptable standard of normality exists. Attempts have been made to correlate findings with the results of ICP and arteriography but neither is a satisfactory criterion. The pitfalls of using these as a "gold standard" have been discussed; the latter, apart from lacking a functional value, also suffers from a paucity of normative data because of ethical constraints. We have found the change in internal calibre of the cavernosal arteries to be of

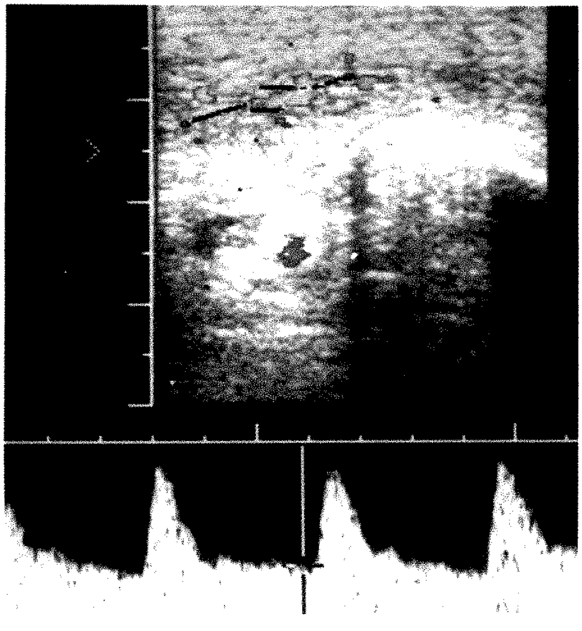

**Fig. 2** Duplex Doppler scan. The cavernosal artery is easily recognisable, allowing accurate positioning of the Doppler sample volume and angle correction. The waveform obtained lies below.

less value in identifying penile artery insufficiency. The arteries in their resting state are particularly susceptible to any adrenergic drive and the internal diameter must frequently be underestimated (Lue *et al.*, 1985b). The calibre following ICP is less affected by the anxiety of the patient but may be altered by direct pressure from the transducer. Calibre changes occur throughout the cardiac cycle and unless measurements are taken at a specified point, further errors may arise. In addition, the resolution of the real time image, though capable of showing considerable detail, does not allow the precise measurement of vessels which are 0.2–1.2 mm in diameter.

Despite the lack of consensus as to which DDU criteria best define arteriogenic impotence, this technique, when used in conjunction with colour mapping, seems to be the method of choice in assessing cavernosal artery flow. However, the search for a better and more reliable parameter of normal and abnormal flow should continue.

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# Cavernosometry: Methodology and Reproducibility with and without Pharmacological Agents in the Evaluation of Venous Impotence

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Summary—Venous impotence can be evaluated by cavernosometry, although this is a controversial issue.

We have evaluated various techniques for cavernosometry: with and without intracavernous papaverine, with different dosages and modalities, with different modes of induction flow and at various intracavernous pressures. A standardised technique was tested and retested in 32 impotent men. If pharmacocavernosometry is accepted as the most reliable test and a maintenance flow <20 ml/min indicates optimal venous occulsion, plain cavernosometry gave 6% false positive and 16% false negative results.

Pharmacocavernosometry was found to be highly reproducible with regard to maintenance flow for patients thought to have optimal venous occlusion and for those with supposed leakage. The induction flow was of no diagnostic value.

After injection of papaverine the maintenance flow became a reproducible parameter for quantifying venous outflow and could be measured with an intracavernous pressure equivalent to systolic blood pressure to minimise cavernous arterial inflow and increase reproducibility.

Perfusion of the penile cavernous spaces with saline was introduced by Newman *et al.* in 1964 to determine the rate of fluid inflow necessary to produce an erection. Dynamic cavernosography for impotence was described by Virag *et al.* (1978) and Michal and Pospichal (1978).

Cavernosometry, *i.e.* measurement of intracavernous pressure during perfusion of the cavernous bodies, is useful in the evaluation of venous impotence. In the literature the diagnostic criteria of cavernosometry have been discussed by analysing induction flow and maintenance flow. Saline was perfused at increasing flow rates until a full erection was obtained. The lowest rate required to induce an erection was known as the induction flow (IF) and the lowest rate needed to maintain an erection was known as the maintenance flow (MF). There has been considerable controversy on venous impotence, with some investigators preferring the IF method (Puyau and Lewis, 1983; Wespes *et al.*, 1984), others the MF method (Malhotra *et al.*, 1986; Buvat *et al.*, 1986; Juenemann *et al.*, 1986) and some recommending the maintenance index (ratio of IF to MF) as a diagnostic indicator of venous impotence (Porst *et al.*, 1987).

The initial perfusion rate and the following increase in flow rate are often not described. The intracavernous pressure at which the MF is measured varies from 80 to 150 mmHg (Wespes *et al.*, 1984; Buvat *et al.*, 1986; Lue *et al.*, 1986; Porst *et al.*, 1987) if recorded/reported at all.

Another major controversy is the use of pharmacological agents in connection with cavernosometry. Some find it of no diagnostic value (Wespes *et al.*, 1986), while others recommend a smooth muscle relaxant (Lue *et al.*, 1986; Desai and Gingell, 1988; Stief *et al.*, 1988).

The aim of the present study was to ascertain which method of cavernosometry would give the most reproducible result.

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## Patients and Methods

A total of 32 men complaining of erectible dysfunction (ED) for at least 6 months were evaluated by the same multidisciplinary approach. They underwent clinical evaluation, neurophysiological investigation (cutaneous perception threshold, bulbocavernous reflex latency time and somatosensory evoked potential of the pudendal nerve), Doppler investigation of the penile arteries (penile brachial index (PBI) <0.7 regarded as arterial insufficiency), papaverine test, cavernosometry, pharmacocavernosometry and pharmacocavernosography.

Cavernosometry was performed twice on 2 separate days to evaluate reproducibility.

### *Technique*

After disinfection and local anaesthesia outside the tunica albuginea both cavernous bodies were punctured, one with a 19 gauge and the other with a 21 gauge butterfly cannula, dorsolaterally just proximal to the corona glandis. The butterfly needles were inserted obliquely and prior to insertion the needles and tubing were filled with saline. The intracavernous position was confirmed by flushing saline (10 ml) through the butterfly needle, which was fixed along the penile shaft with tape.

One cannula (21G) was connected to a Statham transducer for continuous recording of cavernous pressure during the procedure. The other cannula (19G) was connected to a rotating pump (Sarns Blood-pump or Cavropump) to produce an artificial erection.

Artificial erection was induced by perfusion with body temperature physiological saline solution at an initial flow rate of 25 ml/min. Each minute the flow rate was increased stepwise by 25 ml/min until a full erection or maximal pump flow (180 ml/min) was reached. If the intracavernous pressure increased >20 mmHg/min, the flow rate was left unchanged. The flow rate was then reduced to find the maintenance flow, *i.e.* the rate necessary to maintain the erection at the intracavernous pressure equivalent to the systolic brachial blood pressure. In this way the patient's arterial supply to the corpora could be disregarded.

Papaverine 60 mg was injected through one butterfly needle with a tourniquet at the base of the penis. After 5 min the tourniquet was released and vibration was applied for another 5 min. Cavernosometry was then repeated.

After detumescence the 2 cannulas were removed and the patient was asked to apply firm compression for 10 min. In the present study only the MF was considered, MF <20 ml/min being regarded as the optimal caverno-venous occlusive mechanism. This low MF has been reported in control subjects by other investigators (Delcour *et al.*, 1986; Aboseif *et al.*, 1989; Dickinson and Pryor, 1989; Stief *et al.*, 1989). With plain cavernosometry a MF<100 ml/min was regarded as normal venous occlusion (Lewis, 1988). In 4 patients pharmacocavernosometry was first performed with papaverine 30 mg and then a second time with 60 mg.

Prior to this study, 6 patients underwent pharmacocavernosometry in a pilot study to evaluate the effect of different methods of administering papaverine and various dosages. In a further 9 patients the MF rate was measured at intracavernous pressures ranging from 80 to 160 mmHg with different modes of induction flow.

## Results

The 32 patients ranged in age from 25 to 74 years (median 55) and the median duration of erectile dysfunction was 3 years (range 7 months–20 years). There were several possible aetiological factors. Four patients had diabetes mellitus, 4 had undergone previous transurethral procedures, 2 had undergone aorto-femoral bypass surgery, 2 were on antihypertensive therapy, 2 had a history of alcoholism, 2 were heavy smokers, 2 had Peyronie's disease, 1 had had a penile fracture, 1 had had radiation treatment for cancer of the prostate and 1 had neuropathy with decreased sensibility from the umbilicus and distally. The remaining 11 patients had no obvious disorders.

Pharmacocavernosometry revealed that 18 patients (56%) had MF$\geq$20 ml/min. Four patients (12%) had both PBPI<0.7 and MF$\geq$20 ml/min, 5 patients (15%) had PBPI<0.7 alone, 1 had a neurogenic and 1 a psychogenic abnormality, and 3 demonstrated no abnormalities.

Cavernosometry and pharmacocavernosometry were repeated a median of 66 days later (range 2–563).

### *Evaluation of venous leakage with cavernosometry*

Reproducibility was tested in 24 of the 32 patients. Cavernosometry was not completed in 8 patients because of pain during the investigation or fear of pain at repeated investigation. Nine patients had an MF<100 ml/min and 12 demonstrated an MF$\geq$100 ml/min; this was found to be reproducible. Three patients (12%) changed categories, 2 from leakage to normal venous occlusion (110 to 50 ml/min, 180 to 70 ml/min) and 1 patient demonstrated venous leakage at the second investigation (70 to 110 ml/min) (Table 1).

### *Evaluation of venous leakage with pharmacocavernosometry*

Following the injection of papaverine, all 32 patients were tested twice; 11 had an MF$<$20 ml/min, interpreted as optimal venous occlusion, and 21 had an MF$\geq$20 ml/min. These results were reproducible and no patients changed category (Table 2).

Statistically there was a highly significant correlation between test 1 and test 2 with pharmacocavernosometry (Spearmans Rho$=$0.94, $P<0.001$) (Fig.).

### *Cavernosometry versus pharmacocavernosometry*

Of the 11 patients with optimal venous occlusion at pharmacocavernosometry, 2 had an elevated MF (110 and 180 ml/min) with plain cavernosometry ("false positives"). One of these patients demonstrated an elevated MF (110 ml/min) at test 1, normal MF (50 ml/min) at test 2 and after papaverine he showed an optimal venous occlusive mechanism (MF$=$6 ml/min). Of the 21 patients with MF$\geq$20 ml/min at pharmacocavernosometry, 5 had an MF of 60 to 90 ml/min with plain cavernosometry and were therefore considered as having normal venous occlusion ("false negative").

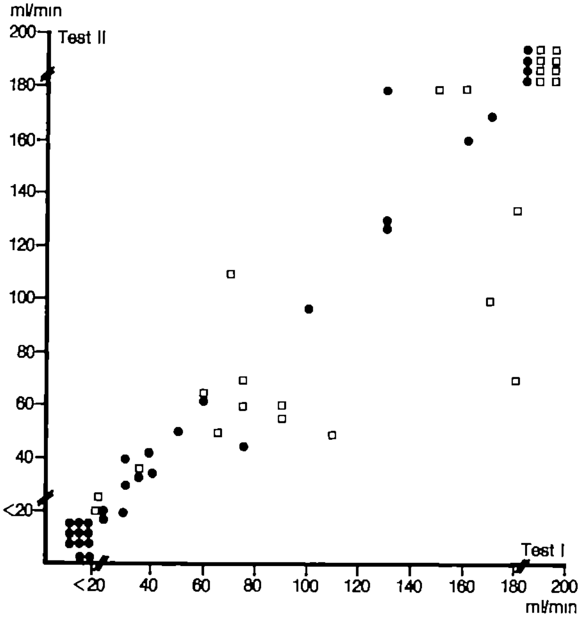

**Fig.** Maintenance flow with pharmacocavernosometry and plain cavernosometry performed twice in 32 and 24 patients respectively. ● Pharmacocavernosometry. □ Cavernosometry. Broken line indicates (1) 11 tests with MF <20 ml/min, not the exact flow values, and (2) induction flow greater than maximum pump flow (180 ml/min) in 12 tests

**Table 1** Results of Cavernosometry without Papaverine

| | *Test 1* | *Test 2* | *Reproducible* |
|---|---|---|---|
| No. of patients | 28 | 24 | |
| Maintenance flow rate | | | |
| Normal (<100 ml/min) | 12 | 11 | 9 |
| Leakage (≥100 ml/min) | 16 | 13 | 12 |
| Not reproducible in 3 patients | | | |
| Normal | (1) | (2) | |
| Leakage | (2) | (1) | |

Test 1 not completed in 4 patients due to pain
Test 2 not completed in 8 patients due to pain or fear of pain.

**Table 2** Results of Pharmacocavernosometry

| | *Test 1* | *Test 2* | *Reproducible* |
|---|---|---|---|
| No. of patients | 32 | 32 | |
| Maintenance flow rate | | | |
| Normal (<20 ml/min) (optimal venous occulsion) | 11 | 11 | 11 |
| Leakage (≥20 ml/min) | 21 | 21 | 21 |

No patient changed category.

### *Pharmacocavernosometry with various dosages of papaverine and different methods of administration*

In 4 patients with MF$\geq$20 ml/min there was a reduction in MF of 15% from papaverine 30 mg over 10 min to 60 mg over 1 min. In 2 patients with optimal occlusion no difference in MF was recorded.

In another 4 patients pharmacocavernosometry was performed with papaverine 30 mg during test 1 and papaverine 60 mg during test 2; and MF was unchanged.

### *Pharmacocavernosometry at different intracavernous pressures*

In 5 patients with MF$<$20 ml/min the MF was the same ($\pm$2 ml/min) in the pressure range 100 to 160 mmHg. With an intracavernous pressure (ICP) of 80 mmHg the MF was approximately 5 ml/min less. In 4 patients with MF$\geq$20 ml/min the MF increased by 10 to 15 ml/min when the ICP was raised from 100 to 160 mmHg.

### *Cavernosometry with different methods of inducing erection*

In 9 patients the mode of saline perfusion was tested to see if the MF was influenced by the induction flow. Neither continuous stepwise increases of 25 ml/min, interrupted increases with a return to initial ICP between increments, nor rapid perfusion (120 ml/min) influenced the MF with pharmacocavernosometry. During plain cavernosometry repeated perfusions tended to lower the IF, but if the patient experienced discomfort or pain the IF tended to be elevated when compared with the initial value.

## Discussion

Normal erectile function requires an intact penile vascular system, including normal arterial inflow into the corpora cavernosa via the profound penile arteries, normal sinusoidal relaxation to allow distension of the cavernous spaces and a decrease in outflow of blood from the cavernous spaces into the venous system (Wagner, 1981; Lue *et al.*, 1983). Maintenance of erection depends on a balance between cavernous arterial inflow and venous outflow. Excessive venous outflow prevents the development of adequate pressure in the corpora cavernosa, resulting in failure to achieve full erection or inability to maintain it.

The venous occlusive mechanism can be evaluated by means of cavernosometry or pharmacocavernosometry. Passive saline perfusion does not relax the intracavernous smooth muscles, as in normal physiological erection, and large amounts of saline are required. The IF depends on the volume of the corpora, the mode of saline perfusion, the MF and the state of contraction in the cavernous smooth muscles. Our observations tend to confirm the findings of other investigators. Repeated perfusions in the unstimulated penis tend to lower the IF. If the patient experiences pain prior to perfusion the penis decreases as a result of smooth muscle contraction (Newman and Reiss, 1984) and discomfort during perfusion results in an elevated IF. In accordance with Stief *et al.* (1988), we found that the induction flow had no value in the evaluation of venous leakage.

Maintenance flow is defined as the lowest rate needed to maintain an artificial erection. This depends on the venous outflow from the cavernous spaces into the venous system and is influenced by the contractile state of the smooth muscles. The MF with saline perfusion alone was shown, in an animal model, to be 5 times higher than the MF in erection induced by both neurostimulation and by papaverine (Stief *et al.*, 1988). Relaxation of the cavernous smooth muscles after cavernous nerve stimulation or papaverine injection resulted in increased venous outflow resistance, which mimics the normal physiological event (Lue *et al.*, 1986).

Plain cavernosometry has been reported to be an accurate assessment of venous leakage (Wespes *et al.*, 1984; Buvat *et al.*, 1986; Malhota *et al.*, 1986; Porst *et al.*, 1987), but the diagnostic value of artificial perfusion was questioned by Newman and Reiss (1984). They found that the rate of false positives and negatives devalued the test.

The use of pharmacological agents has been the subject of much discussion. Wespes *et al.* (1986), Delcour *et al.* (1986) and Wespes and Schulman (1987) claimed that injection of papaverine failed to give additional information and Lewis (1988) stated that cavernosometry was a diagnostic tool perhaps best used without pharmacological agents. Basic research into erectile physiology (Juenemann *et al.*, 1986; Stief *et al.*, 1988) and evaluation of impotent men (Lue *et al.*, 1986; Desai and Gingell, 1988; Stief *et al.*, 1989) resulted in recommendations to use papaverine at cavernosometry.

Our results indicate that plain cavernosometry was not reproducible in 3/24 patients (13%). In another 4 patients the high perfusion rates were painful and MF could not be evaluated. If a MF $<20$ ml/min during pharmacocavernosometry indicates optimal venous occlusion (Delcour *et al.*, 1986; Dickinson and Pryor, 1989; Stief *et al.*, 1989), then in 6% and 16% of patients the diagnoses obtained by plain cavernosometry were false positive and false negative respectively.

Our findings with different dosages of papaverine and modes of administration show that papaverine 60 mg is sufficient to relax the cavernous smooth muscles. When these muscles are relaxed the MF becomes independent of the mode of induction. In patients with an optimal venous occlusive mechanism, the MF is for diagnostic purposes the same in the pressure range 100 to 160 mmHg; below 100 mmHg the patient's cavernous arteries may contribute, depending on the systolic blood pressure. In patients with venous leakage we found an increase in flow rate (10–15 ml/min) when the ICP was raised from 100 to 160 mmHg. The more elevated the MF, the more the flow rate increased with raising ICP. When using a standardised technique such as ours, this variation is minimised and does not affect the reproducibility. This standardisation is necessary (1) when cavernosometry is used to evaluate the result after venous leakage surgery, (2) when testing the effects of various drugs and (3) when comparing the incidence and prevalence of venous leakage. We found highly reproducibile results with pharmacocavernosometry for patients with optimal venous occlusion and for those with venous leakage. These results are in contrast to the findings of Lewis and Parulkar (unpublished observations), who found fluctuating values of MF with pharmacocavernosometry. We agree with Lue *et al.* (1986) and Stief *et al.* (1988) that cavernosometry and cavernosography should be performed after papaverine injection. The amount of saline perfusion necessary to produce an artificial erection is not only less after papaverine, but the MF rate is a reliable and reproducible parameter to quantify the caverno-venous outflow.

In accordance with Wespes *et al.* (1986), Stief *et al.* (1989) and Aboseif *et al.* (1989), it appears that $\mathrm{MF} \geq 20$ ml/min during pharmacocavernosometry is equivalent to non-optimal venous occlusion or leakage. However, the diagnostic and prognostic value of this cut-off value remains to be shown.

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# Histological Grading of Squamous Cell Carcinoma of the Penis: A New Scoring System

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Summary—A system of histological grading based on retrospective analysis of 239 patients with squamous cell carcinoma of the penis is presented. A new scoring system with 4 histological grades was used. The results of this study confirm previous reports that penile cancer is usually a highly (50%) or moderately (29%) differentiated squamous cell carcinoma. Poorly differentiated carcinomas and cancers of other types are very rare. The new grading system was found to be practical and a correlation between histological grade, clinical findings and prognosis was established. Patients with grade 1 tumours had an exceptionally favourable prognosis, with more than 80% being long-term survivors; for these patients, treatment with delayed side effects should be avoided and new forms of treatment should be explored.

Penile cancer almost always presents as squamous cell carcinoma, with sarcomas and other histological types being rare (Khezri *et al.*, 1978).

Most carcinomas of the penis arise from the epithelium of the glans or from the inner surface of the prepuce, occasionally from both of these structures. It can also originate in the corona or the sulcus coronarius (Newaishy and Deeley, 1968; Brühl, 1977). The tumour develops as a warty mass with induration, ulceration or plaque-like change. Verrucous carcinomas are usually highly differentiated and less infiltrative, while ulcerative tumours are poorly differentiated and readily infiltrate deeper structures (Marcial *et al.*, 1962; Evans, 1966).

There is no specific grading system for penile cancer, although use has been made of the grading system for squamous cell carcinoma of the skin based on cell maturation (Broders, 1928). In this system, the degree of keratinisation is the principal feature. Edmundson (1948) suggested that grading should be based on the least differentiated portion after examination of several sections. It is now recognised that it should also be based on the degree of atypia of the tumour cells and the depth of penetration. Four grades are usually involved (Frew *et al.*, 1967).

In order to establish the possible association between histological differentiation and location of the primary tumour, as well as the anatomical extent (staging) of this cancer, histological analysis and a system of histological grading were used, based on a retrospective study of 239 patients with squamous cell carcinoma of the penis. The relationship between histological grading, clinical behaviour and prognosis was examined.

## Patients and Methods

Histological specimens of the primary tumours and/or metastases were obtained in 251 cases (91% of the basic series of 275 patients). These were re-examined and reclassified. One lesion proved to be a metastasis to the penis from a prostatic carcinoma, 1 was a malignant melanoma, 1 an adenocarcinoma, 4 were sarcomas and 5 were considered to be benign lesions. After exclusion of these 12 patients, the final number of squamous cell carcinomas of the penis in the series was 239.

Assessment of the histological differentiation grade was based on 4 criteria: the degree of keratinisation, the number of mitotic cells/high power field (×400), the presence of cellular atypia

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and the presence of inflammatory cells. The least differentiated area of the specimen was selected, as suggested by Edmundson (1948). The histological samples were re-examined 3 times by 2 authors. The final score was the median value of all 6 primary scores. Slight differences in scoring results were found in less than 10% of cases.

Scores for the different parameters were as follows:

*Degree of keratinisation*

3 points: horn pearls complete or keratin in 75% or more of the cells.
2 points: horn pearls incomplete or keratin in 50 to 75% of the cells.
1 point: no horn pearls, keratin in 25 to 75% of the cells.
0 points: no horn pearls, keratin in less than 25% of the cells and difficulty in making the diagnosis of squamous cell carcinoma.

*Mitotic cells*

The score was given as the number of mitotic cells/high power field ( × 400).

3 points: 0–2 mitotic cells/field.
2 points: 3–5 mitotic cells/field.
1 point: 6–9 mitotic cells/field.
0 points: 10 or more mitotic cells/field.

*Cellular atypia*

Cellular and nuclear atypia were analysed on the basis of the intensity of hyperchromacy of nuclei, the size of nucleoli and the presence of intercellular bridges. The score was given as the number of atypical cells/high power field ( × 400).

3 points: few atypical cells/field.
2 points: moderate number of atypical cells/field.
1 point: many atypical cells/field.
0 points: all cells atypical.

*Inflammatory cells*

1 point: inflammatory cells (lymphocytes) present.
0 points: no inflammatory cells present.

After the summation of all scores, the histological grade was established as follows:

Grade 1: 8–10 points.
Grade 2: 5–7 points.
Grade 3: 3–4 points.
Grade 4: 0–2 points.

The survival rates were calculated by the actuarial method. Relative survival rates were used, defined as ratios of the observed and expected rates. The expected survival rates were obtained from the life tables for the total Finnish population over the period of 1956 to 1965.

## Results

Tumours with a high degree of differentiation (grade 1) formed the largest group (50%), followed by grade 2 (29%) (Table 1). The grade distribution of tumours was broadly similar in all age groups but the proportion of grade 3 and 4 tumours was somewhat lower in patients aged 70 years or more (14%) than in other age groups (21–25%) (Table 1).

There was a correlation between clinical stage and histological grade. Highly and moderately differentiated tumours (grades 1 and 2) were over-represented in clinical stages I (83%) and II (86%) compared with clinical stages III (67%) and IV (52%) (Table 2). The highest proportion of poorly differentiated grade 4 tumours (24%) was found in stage IV.

Tumours originating from different sites of the penis presented differences in the grade distribution. Up to 90% of tumours of the prepuce were grades 1 and 2 (the entire series 79%) and there was a higher than average proportion of grades 3 and 4 among tumours of the shaft (43% vs 21%) (Table 3).

Histological grade appeared to be a valuable prognostic factor. The 5-year and 10-year relative survival rates were highest among patients with highly differentiated (grade 1) tumours, 83 and 82% respectively, and lowest among those with poorly differentiated lesions (grade 4), 30 and 40% respectively (Fig.). There was no significant difference in the survival rates between grades 2 and 3 (Fig.).

## Discussion

Histological grading is of importance to clinicians

**Table 1** Distribution of 239 Squamous Cell Carcinomas of the Penis by Histological Grade and Age

| | *Age group (years)* | | | | |
|---|---|---|---|---|---|
| | *20–49* | *50–59* | *60–69* | *≥70* | *Total* |
| *Histological grade* | *No (%)* | *No (%)* | *No (%)* | *No. (%)* | *No. (%)* |
| 1 | 28 (54) | 28 (48) | 27 (47) | 37 (51) | 120 (50) |
| 2 | 11 (21) | 16 (28) | 18 (32) | 25 (35) | 70 (29) |
| 3 | 10 (19) | 10 (17) | 9 (16) | 8 (11) | 37 (15) |
| 4 | 3 (6) | 4 (7) | 3 (5) | 2 (3) | 12 (5) |
| Total | 52 (100) | 58 (100) | 57 (100) | 72 (100) | 239 (100) |

**Table 2** Distribution of 239 Squamous Cell Carcinomas of the Penis by Histological Grade and Clinical Stage

| | *Stage** | | | | | |
|---|---|---|---|---|---|---|
| | *I* | *II* | *III* | *IV* | *TXNX* | *Total* |
| *Histological grade* | *No. (%)* | *No (%)* | *No. (%)* | *No. (%)* | *No. (%)* | *No. (%)* |
| 1 | 73 (58) | 29 (44) | 13 (48) | 4 (19) | 1 (50) | 120 (50) |
| 2 | 30 (24) | 27 (42) | 5 (19) | 7 (33) | 1 (50) | 70 (29) |
| 3 | 19 (15) | 6 (11) | 7 (26) | 5 (24) | — | 37 (15) |
| 4 | 3 (2) | 2 (3) | 2 (7) | 5 (24) | — | 12 (5) |
| Total | 125 (100) | 65 (100) | 26 (100) | 21 (100) | 2 (100) | 239 (100) |

* As suggested by Maiche and S. Pyrhönen (1990).

**Table 3** Distribution of 239 Squamous Cell Carcinomas of the Penis by Histological Grade and Localisation

| | *Localisation* | | | | | |
|---|---|---|---|---|---|---|
| | *Glans* | *Prepuce* | *Glans and prepuce* | *Shaft or all penis* | *Unknown* | *Total* |
| *Histological grade* | *No. (%)* | *No. (%)* | *No. (%)* | *No. (%)* | *No. (%)* | *No. (%)* |
| 1 | 69 (50) | 39 (63) | 6 (33) | 4 (29) | 2 (22) | 120 (50) |
| 2 | 40 (29) | 17 (27) | 7 (39) | 4 (29) | 2 (33) | 70 (29) |
| 3 | 23 (16) | 6 (10) | 3 (17) | 3 (21) | 2 (33) | 37 (15) |
| 4 | 7 (5) | — — | 2 (11) | 3 (21) | — — | 12 (5) |
| Total | 139 (100) | 62 (100) | 18 (100) | 14 (100) | 6 (100) | 239 (100) |

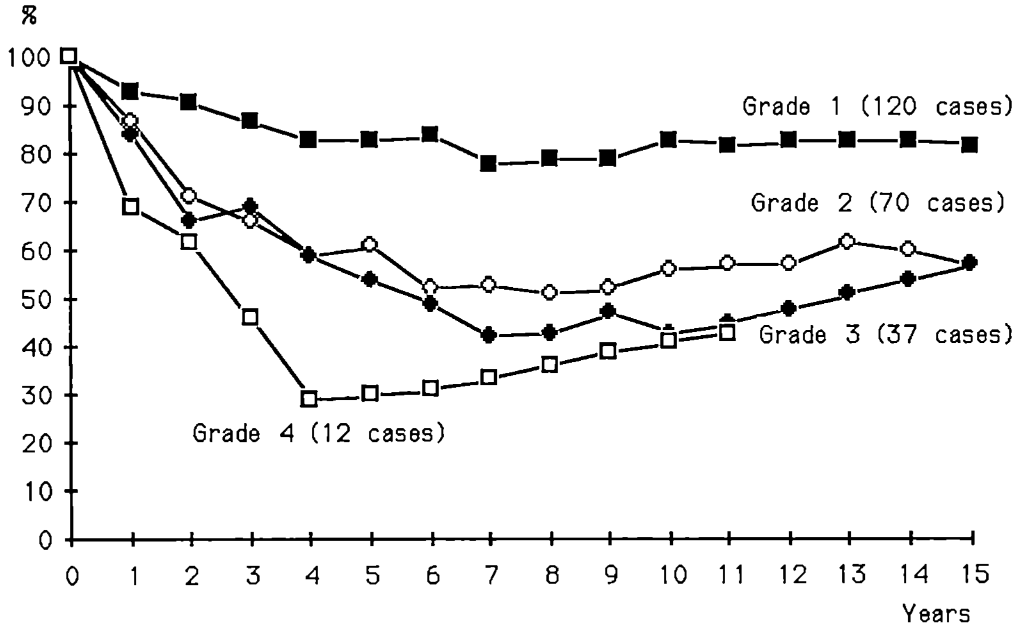

**Fig.** Relative survival curves of 239 patients with squamous cell carcinoma of the penis, according to histological grade.

when planning treatment for cancer patients. The grading system should be practical and should provide valid information regarding the prognosis. In the present study we have applied a new scoring system for the histological grading of squamous cell carcinoma of the penis and analysed its practicability in 239 patients.

In previous studies, histological grading of penile carcinoma was based mainly on cell maturation (Broders, 1928; Edmundson, 1948) and other histological aspects (which could be relevant to the clinical behaviour of a tumour) were omitted. Most of the previous analyses divided squamous cell carcinomas of the penis into 3 or 4 categories (Table 4) and in 2 reports only 2 categories were used (Colby and Smith, 1931; Staubitz *et al.*, 1955). The common feature in all of these studies was the observation that about half of the squamous cell carcinomas of the penis were highly differentiated (grade 1). However, an exception to this was a report of Ugandan patients where only 25% of patients had highly differentiated carcinomas (Schmauz, 1973). Poorly differentiated tumours usually represented 10 to 26% of all cases (Table 4). The similar results in the distribution into histological grades reported in these previous studies revealed that expert pathologists in different centres had similar rules for grading squamous cell carcinomas. This, however, does not exclude the possibility that in individual cases, remarkable differences could arise if the same samples were to be graded by several pathologists. We feel that the scoring system described in this report makes it possible to avoid subjective bias in grading and we considered it useful to compare the results of this sytem with clinical parameters.

In the present study, there was no significant difference between the groups in grade distribution according to age, as suggested by Schmauz 1973, who reported that patients with poorly differentiated squamous cell carcinoma had a higher median age.

As expected, histological grade correlated with the clinical stage. Patients with poorly differentiated tumours tended to have advanced disease. Histological grade had a somewhat different pattern, depending on the localisation of the primary tumour. Almost half of the tumours originating in the shaft were grades 3 or 4, while only 10% of tumours located in the prepuce were in these grades. This evidently reflects some differences in growth pattern for carcinomas at different sites, which might also have some relevance to management of the patient.

**Table 4** Distribution of Histological Grades in Squamous Cell Carcinoma of the Penis in Various Studies

| *Author(s)* | *No of patients* | *Histological grades (%)* 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Basset (1952) | 62 | 45 | 44 | 11* | — |
| Ekström and Edsmyr (1958) | 195 | 44 | 31 | 26* | — |
| Frew *et al.* (1967) | 44 | 59 | 20 | 14 | 7 |
| Schmauz (1973) | 418 | 28 | 50 | 22* | — |
| Jensen (1977) | 286 | 40 | 36 | 21 | 3 |
| Khezri *et al.* (1978) | 63 | 52 | 35 | 11 | 2 |
| Fraley *et al* (1985) | 37 | 54 | 35 | 11* | — |
| Present study | 239 | 50 | 29 | 15 | 5 |

* Distributed according to a system of 3 histological grades.

Finally, we analysed the prognosis and found that it correlated with the histological grading. Long-term follow-up enabled a better evaluation to be made of the clinical impact of histological grading than was possible in the earlier studies on penile cancer. The prognostic value of histological differentiation was clearly demonstrated in the present study. Patients with grade 1 tumours had an exceptionally favourable prognosis and more than 80% were long-term survivors. As expected, prognosis was poorer in patients with poorly differentiated tumours.

These results show that our histological grading system for squamous cell carcinoma of the penis was practical and clinically useful. Histological grade may be an important factor in planning treatment. Patients with a grade 1 tumour, for instance, are long-term survivors and delayed side effects of treatment such as urethral stricture, fibrosis, necrosis, elephantiasis, teleangiectasia and painful erection or impotence must be seriously considered. In these patients, new forms of treatment should be explored, as suggested by Pyrhönen *et al.* (1991).

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# Relationship between Urease-producing Bacteria, Urinary pH and Encrustation on Indwelling Urinary Catheters

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Summary—In 11 patients with long-term indwelling catheters the amount of catheter encrustation and urinary pH were measured and the urine regularly cultured over a prolonged period of time (median of 7 periods of 3 weeks). The mean urinary pH was related to the persistent presence of urease-producing micro-organisms (*P. mirabilis*) and urinary pH governed the precipitation of catheter encrustation. The critical pH appeared to be around 6.8. In patients with a mean urinary pH below this level the encrustation was minute ($\leq 2.9$ mg phosphate). In patients with a mean urinary pH above 6.8 it was considerable but with a marked interindividual variation (35.5–138.7 mg phosphate). The composition of the encrustation was also strongly pH-related, with a much higher proportion present as magnesium ammonium phosphate in patients with a mean urinary pH above 6.8. The persistent presence of urease producers was not associated with a high pH or a more pronounced precipitation of phosphate in all patients. The amount of encrustation thus appears to depend not only on the presence of urease-producing micro-organisms but also on individual factors such as urinary composition.

The urinary tract of patients with long-term indwelling catheters is invaded by bacteria but it is frequently difficult clinically to distinguish colonisation from infection. The usual causative organisms are aerobic bacteria, mostly urease-producing species such as *Proteus mirabilis* and *Klebsiella pneumoniae* (Eddeland and Hedelin, 1983). Urease activity may lead to urine alkalisation. Secondary to this pH increase, urine is supersaturated with magnesium ammonium phosphate (MAP) and calcium phosphate (CaP) (Robertson and Nordin, 1976). These salts tend to precipitate on the catheter and its lumen, resulting in local irritation and catheter blockage (Slade and Gillespie, 1985). In previous studies, a large inter-individual variation in the tendency to precipitation of catheter encrustation has been observed (Bruce *et al.*, 1974; Hedelin *et al.*, 1985b). The amount of material precipitated was related to the time the catheter could remain *in situ* (Hedelin *et al.*, 1985b). Marked precipitation leading to frequent catheter changes was also found in a few patients infected with bacteria without urease production. Urinary pH was not measured, however, and cultures were performed only by conventional routine methods.

The aim of the present study was to correlate urinary pH with the precipitation of catheter encrustation. The urinary pH in patients with long-term indwelling catheters was therefore monitored and the material precipitated on the catheters was measured and analysed. An additional aim was to detect any unusual urea-splitting bacteria in catheter urine samples with a raised pH but without growth of urease-producing bacteria on routine culture. The bacteriology laboratory was prepared to carry out a more thorough cultural procedure should a sample with high pH not grow any of the common urease-producing bacterial species.

## Patients and Methods

The study was made in a hospital with 500 beds for long-term care and rehabilitation. Male and female

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patients with a probable long-term need for an indwelling catheter and an expected survival of >6 months were included. All had had an indwelling catheter for at least 3 months and were provided at the start of the study with a teflon-coated latex catheter (Bardcomatic, Bard Ltd) 14 or 16 F. The catheter was connected to a drainage bag, which was replaced under non-sterile conditions and therefore a strictly closed drainage system was not maintained. The catheters were routinely changed every third week and any catheter changes necessary in between were recorded. In the event of catheter obstruction, the catheter was rinsed twice with 50 ml saline. If this did not restore function, the catheter was changed. No patient received antibiotics, methenamine hippurate or ascorbic acid during the study.

Urinary pH was measured at 07.00 and 15.00 on 2 days every week using indicator strips with pH intervals of 5.4–7.0 and 6.4–8.0 respectively (Merck, Darmstadt, Germany). The urine volume was measured on the same 2 days and a urine sample was sent for bacterial culture once every third week. To obtain urine samples for culture and pH measurement, the catheters were clamped for 15 min. After release of the clamp, the first 10 ml of urine were discarded. Urine was thereafter collected and the pH measured immediately. All samples were refrigerated during transport. Routine urinary culture was performed with calibrated loops delivering 3 µl and 2 plain media: a non-selective agar, also used for susceptibility testing (PDM ASM agar, AB Biodisk, Solna, Sweden), and an agar selective for Gram-negative rods (lactose bromothymol blue agar). Isolated bacterial strains were identified by standard methods (Lenette *et al.*, 1985). This included a tube with 5 ml urea broth and phenol red as indicator, turning from yellow to red at pH 6.8–6.9, thus detecting the presence of urease-producing micro-organisms.

Immediately after extraction, the catheters were placed in plastic containers filled with 100 ml 0.5 M HCl to dissolve the encrustation. The containers were then shaken continuously for 2 h in a water bath kept at 37°C. The HCl solution was then filtered through an 0.22 µm pre-weighed Millipore filter with a constant vacuum pressure.

The filter containing the precipitated material was dried overnight at 40°C and weighed again. The difference between the 2 measurements constituted the dry weight of the insoluble part of the catheter encrustation and henceforth termed the dry weight.

The phosphate and magnesium content of the 0.5 M HCl solution was measured using a colorimetric method and atomic absorption spectrometry respectively (Zilversmith and Davies, 1950; Savory *et al.*, 1969). The amount of magnesium precipitated was assumed to be present as MAP, the non-magnesium-bound phosphate being assessed as CaP. This assumption has been validated in a previous study (Hedelin *et al.*, 1985a).

The means, standard deviations and coefficients of variation were calculated using conventional statistical methods.

## Results

Eleven patients (3 females) were followed for between 5 and 10 3-week periods (median 7 periods). The age of the patients ranged between 66 and 93 years (Table).

Six patients had persistent growth of *Proteus mirabilis* and 4 patients had persistent growth of *Escherichia coli*. From all of these 4 patients, urease-producing micro-organisms were also occasionally cultured. In patient No. 11, *E. coli* was cultured during the first 4 3-week periods and urease-producing *Klebsiella pneumoniae* during the last 4 3-week periods.

The mean afternoon pH was lower, or equal to, the mean morning pH in all patients.

In the 4 patients with persistent growth of *E. coli*, the mean afternoon pH was below 5.40, with a small inter-sample variation. In the patients with growth of *Proteus mirabilis*, the mean afternoon pH was above 6.11 and the mean morning pH above 6.66, mostly with a large variation between different samples from the same person.

The amount of phosphate precipitated depended on the mean urinary pH. This applied both to the morning and to the afternoon pH (Fig. 1) (Table). The critical pH appeared to be between 6.7 and 6.8. The precipitation was 10 times greater in individuals with a urinary pH above 6.8 than in those with a mean pH below 6.7. The proportion present as MAP (presented as the ratio between non-Mg-bound and Mg-bound phosphate) was also strongly pH-related, satisfying a linear equation (Fig. 2). In patients with a mean pH below 6.7 the ratio was well above 1, while in patients with a pH above 6.8 it was 0.77 or below (Table).

Urinary pH, and thus the phosphate precipitation, was linked to the presence of urease-producing micro-organisms. All patients with a mean pH >6.6 had persistent growth of *P. mirabilis*. The persistent presence of urease-producing micro-

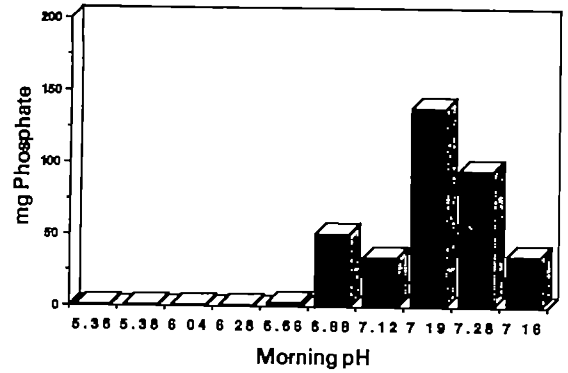

**Fig. 1** Mean amount of catheter encrustation (mg phosphate) related to mean morning pH in patients with long-term indwelling catheters

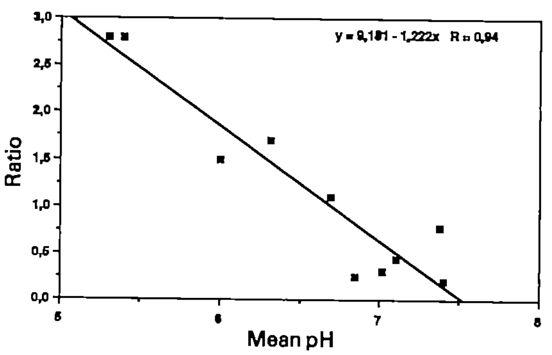

**Fig. 2** Proportion of catheter encrustation in patients with indwelling catheters present as CaP compared with MAP (Ratio between non-Mg-bound and Mg-bound phosphate in relation to mean morning pH).

organisms did not, however, always imply an alkaline urine. One patient, No. 5, had persistent growth of *P. mirabilis* and reached a mean morning pH of 6.7 but also had a very low precipitation of catheter encrustation (Table).

Catheter encrustation was also observed in the patients with persistent growth of *E. coli*. Growth of urease-producing micro-organisms was also detected on some occasions in all of them.

There was no correlation between the precipitation of phosphate and the frequency of catheter changes or the urine volume (Table).

The frequency of catheter changes tended to be lower in patients with a mean urinary pH below the critical limit. These individuals had a mean frequency of unscheduled changes of 0.5 per 3-week period, compared with 1.4 in patients with a mean pH above 6.8. The dry weight of the insoluble part of the encrustation tended to be higher in patients infected with urease-producing micro-

**Table** Results of Investigations

| *Patient no.* | *Sex* | *Age (years)* | *Mean morning pH ± SD* | *Mean afternoon pH ± SD* | *Bacterial flora + = strain with urease activity* | | *Phosphate/ catheter (mg)* | *Ratio** | *Insol. precip Dry weight (mg)* | *Mean urine/ volume/24 h* | *Catheter changes per period* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 86 | 5.36±0.18 | 5.35±0.21 | *E. coli*<br>(*P. mirabilis* × 1)<br>(*Klebsiella* × 1) | –<br>(+)<br>(+) | 1.1 | 2.8 | 5.6 | 1072 | 0 |
| 2 | M | 89 | 5.35±0.13 | 5.34±0.19 | *E. coli*<br>*Staph. aureus*<br>(*P. mirabilis* × 1) | –<br>–<br>(+) | 1.3 | 2 8 | 3.5 | 954 | 0 |
| 3 | F | 67 | 6.04±0.39 | 5.37±0.26 | *E. coli*<br>(*Klebsiella* × 1) | –<br>(+) | 1.1 | 1.5 | 1.4 | 1021 | 1.3 |
| 4 | M | 89 | 6.28±0.61 | 5.29±0.38 | *E coli*<br>(*P mirabilis* × 1) | –<br>(+) | 0.7 | 1.7 | 3.0 | 1840 | 0.8 |
| 5 | M | 79 | 6.66±0.66 | 6.11±0.20 | *P. mirabilis* | + | 2.9 | 1 1 | 4.0 | 1587 | 0.4 |
| 6 | M | 95 | 6.88±0.19 | 6.87±0.18 | *P mirabilis*<br>*Klebsiella* | +<br>+ | 51.0 | 0.25 | 27.8 | 1268 | 0.8 |
| 7 | M | 89 | 7.12±1.18 | 6 63±0.98 | *P mirabilis* | + | 34.3 | 0.30 | 2.6 | 1054 | 3.6 |
| 8 | M | 81 | 7.19±0 81 | 6.68±0.42 | *P. mirabilis* | + | 138.7 | 0.44 | 11.0 | 1078 | 0.3 |
| 9 | M | 91 | 7.28±1.08 | 6.59±0 85 | *P. mirabilis* | + | 95.4 | 0.77 | 5 6 | 1175 | 0.8 |
| 10 | M | 83 | 7 16±0.91 | 6.90±0.92 | *P mirabilis*<br>*E. coli* | +<br>– | 35 5 | 0 20 | 7.7 | 1120 | 1 6 |
| 11 | F | 84 | | | | | | | | | |
| First 3 months | | | 5.13±0.26 | 5.13±0 23 | *E. coli*<br>Enterococci | –<br>– | 0.97 | 1.20 | 3.4 | 779 | 0 |
| Second 3 months | | | 5.72±0.65 | 5.62±0.58 | *E. coli*<br>*Klebsiella* | –<br>+ | 107.4 | 0.42 | 11.1 | 625 | 0 |

* Ratio = non-Mg-bound to Mg-bound phosphate.

organisms (*P. mirabilis*). Patient No. 11 was infected with *E. coli* during the first half of the study and minimal encrustation was present on the extracted catheters. During the second part of the study, she became infected with urease-producing *K. pneumoniae*. Her mean pH increased very little and stayed below 5.8 but the encrustation on the catheters increased very markedly.

## Discussion

Urinary pH was related to the persistent presence of urease-producing *P. mirabilis* and the precipitation of phosphate on the catheters was linked to urinary pH. A mean morning urinary pH of 6.7 to 6.8 appeared to be critical both for the amount precipitated and for the composition of the precipitate. The phosphate precipitated was thus present mainly as CaP in patients with a mean urinary pH below 6.7 and mainly as MAP in patients with a mean pH above 6.8. A small but measurable amount of precipitation was also noted on catheters from patients permanently colonised with *E. coli* and with a low mean urinary pH.

The presence of urease-producing bacteria was, however, not necessarily linked to marked precipitation of phosphate. This was shown by patient No. 5 (Table). Despite persistent growth of *Proteus* mirabilis, his mean urinary pH stayed below 6.8 and the precipitation observed was small.

That persistent colonisation with a urease-producer is not always associated with a high pH, and that a high mean pH is not a prerequisite for phosphate precipitation, was demonstrated by patient No. 11. In this patient, the colonisation with a urease-producer that occurred during the study increased mean urinary pH to only 5.7 but was still associated with a marked degree of precipitation.

Urinary pH is subject to a diurnal rhythm with the urine least acid after awakening (Conroy and Mills, 1970). This was also the case in these infected patients. Both morning and afternoon pH was strongly related to the precipitation of encrustations, MAP being the major component at higher urinary pH.

Patients with long-term indwelling catheters can be divided into 2 groups: blockers, with massive precipitation of catheter encrustation, and non-blockers, with low precipitation (Kunin *et al.*, 1987). A prerequisite for blockers is infection with urease-producing bacteria (*P. mirabilis*) at sufficient strength to raise the pH to 6.8 or above. The results of our study show that if the mean pH remains below this level, precipitation will usually be low. If the mean pH is higher, precipitation will be much more pronounced and the patient risks becoming a blocker.

The volume of the precipitate, once the critical pH level was reached, did not depend on the degree of the increase in pH (Table). Even with a similar mean urinary pH, precipitation differed 4-fold. Experimental studies have shown that the urease-induced crystallisation of CaP and MAP in human urine is related to the urinary content of calcium and magnesium (Hugosson *et al.*, 1990). Variations in urinary composition, like differences in urinary calcium and magnesium, could thus be another explanation for the existence of blockers and non-blockers.

The formation product for CaP is exceeded at a pH between 6.5 and 7.0, depending on the urinary composition (Robertson and Nordin, 1976). The formation product for MAP is exceeded at a somewhat higher pH (Elliot *et al.*, 1958). In this study, the proportion of the precipitate present as MAP also increased markedly with urinary pH (Fig. 2). The critical pH level for MAP precipitation was lower in our study (6.7–6.8). This finding merits attention since it shows the relationship between urinary pH and the precipitation of MAP and CaP in an *in vivo* context. The previous studies were based on *in vitro* experiments and calculations.

The urease-induced pH increase depends on the number of infecting micro-organisms, their potency as urea splitters and for how long they are allowed to exert their effect in urine. The pH of the uninfected urine from the kidneys and urinary buffer capacity may also be of importance. The first step in preventing catheter encrustation must be the prevention of infection and this is virtually impossible during long-term catheterisation. A second line of defence would be to alter the urinary composition in a way that reduces the urease-induced crystallisation. Possible methods of evaluation include the lowering of urinary calcium and magnesium. Increasing the urinary buffer capacity in order to lower the urease-induced pH rise may, theoretically, also be of benefit. Urine acidification could be another way to diminish precipitation but may be difficult to achieve on a long-term basis.

One of the aims of this study was to find an explanation for the previous observation that catheter encrustation may develop even in patients with persistent growth of only *E. coli*. Four of our 11 patients were in this category. All had an acid urinary pH, however, which makes the presence of urease producers not detected by conventional culture routines unlikely. The precipitation on the catheters in these patients was low and chiefly composed of CaP. This is in contrast to those patients permanently colonised by urease producers. It cannot be ruled out that the precipitation was due to other, as yet unexplained, mechanisms not related to urease activity. The low urinary pH and the very small proportion of the precipitation present as MAP in this group suggest this possibility.

Few studies concerning methods of measuring catheter encrustation have been published (Bruce *et al.*, 1974; Hedelin *et al.*, 1984). The method we have developed, with immediate dissolution of the encrustation in acid, was designed to be easy to use in a busy ward and still give valid results. We feel that determination of the phosphate portion of the encrustation can be performed with satisfactory results. The relevance of the acid-insoluble part of the encrustation is more difficult to define. It probably consists of organic material precipitated on the catheters, such as desquamated epithelial cells, leukocytes and bacteria.

This study has confirmed that persistent infection with *P. mirabilis* is associated with an elevated urinary pH and pronounced precipitation of catheter encrustation. This precipitation shows marked inter-individual variation and persistent growth of *P. mirabilis* is, in certain patients, not associated with either a pH increase or pronounced precipitation.

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# The Winchester Experience with the TDS Hospital Information System

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Summary—The Royal Hampshire County Hospital is a pilot site for the Resource Management Initiative. It is also the pilot site within the Wessex Region for the Hospital Information System (HIS).

We have pursued an ambitious, integrated information system strategy within the hospital. This has been planned and most of it implemented within a short timescale. Although some of the remaining difficulties are technical, the greatest challenges relate to people, their reactions to the introduction of new technology and the need to acquire new skills. The training and development of staff become critical. The importance of an effective management structure with major medical and nursing involvement has been, and will remain, crucial to our continued progress.

## What is a Hospital Information System?

This system combines a Patient Administration System (PAS) with an Order/Communication System (OCS). The former holds demographic data on all patients who have attended the hospital. It also holds waiting lists and pre-admission lists. In-patients can be located from any terminal in the hospital (currently about 200). Orders can be placed with service departments (physiotherapy, X-ray, etc.) and where interfaces with departmental systems exist, results are available on line. Other departments or individuals can send messages. All prescribing of drugs and intravenous fluids is done on the system. Consultants can compile personal order sets which indicate groups of tests that will usually be required in particular situations, for instance patients admitted for prostatectomy. They may also include drugs, for instance investigations and analgesia for patients admitted with renal colic. The nursing component contains admission assessments, care plans and nursing dependency, as well as access to orders and prescribing from medical staff. Staff can also order all supplies.

On discharge a short summary including diagnosis, operative procedure, drugs prescribed on discharge and plans for follow-up can be generated. There is a facility for free text if necessary. All of the data remain live for 45 days to allow diagnostic and procedure coding using the International Classification of Diseases 9th revision (ICD9) and the Office of Population Censuses and Surveys 4th revision (OPCS 4).

A basic data set is retained live and the rest is purged. These data are stored on tape and are available within 24 h. Hard copy of important information is retained in the clinical notes. Holding the information on the live system in this way does not alter the operation speed significantly.

In the main, choices are made from menus by lightpen selection and there is minimal need of keyboard skills. Each lightpen choice takes about 1 s.

## Why Do we Need One?

The main purpose has been to improve the efficiency and effectiveness of the delivery of patient care. The Hospital Information System and related departmental systems, such as Radiology and Pharmacy, are designed to improve communications, save time and enable some control of quality to be built into everyday activity.

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These patient-based operational systems generate an extensive data base and when merged with financial and manpower data, produce detailed information which can form the basis for audit.

## Planning and Implementation

At the start, the project was managed as a regional contract using a firm of management consultants. The initial work, which should not need to be repeated, was an extensive translation of US terminology. This began in January 1987.

The PAS was introduced in September 1987 on to 100 workstations throughout the hospital after training 962 staff.

By this stage a number of disadvantages to the regionally managed contract were beginning to appear. We needed to develop the skills to construct and change the screens amongst a group of hospital staff. We needed local skilled technical support and the ability to deal directly with the suppliers of the hardware and software to help us develop these skills.

A HIS project team was established and the whole project was now managed by the Hospital Management Board, which comprised the Unit General Manager, Assistant Unit General Manager, who had particular responsibilities for this project, and Resource Management Initiative, 8 Clinical Directors, Finance Manager and Director of Nursing Services.

Supplies ordering was introduced across the hospital in September 1988. Prescribing was introduced to General Surgery and Urology in January 1989 and the OCS and nursing systems followed shortly after. Over the course of the next year, it was extended to other ward areas—the last being medicine. The pharmacy component proved the most difficult and after the initial group of wards, was always introduced last.

## Training and Support

With the introduction of PAS, 960 staff were trained by a small team. We realised that a proper planned resource was required for the introduction of the OCS and Nursing Systems.

Six weeks before each ward implementation a member of staff was seconded to the HIS team and continued in this role until 6 weeks after the implementation. Training in an area began with a seminar from the Unit General Manager. The seconded member of staff then ran a combination of computer-based training and hands-on experience in the "training hospital", using dummy patients, together with a seminar on paper management.

Once the system is live, training is replaced by support. The HIS team provided 24-h cover in shifts for the first week. This reduced to 16-h cover in the second week, with the remaining 8 hours covered by bleep.

The role of the seconded persons is very important at this stage. They act as local trouble-shooters for staff on the wards and help to channel suggestions and improvements to the HIS team. Perhaps most importantly, they are a focus for the reactions of the new users to the system and help to gauge how the implementation is going in that particular area.

## Realising the Benefits

The decision was made that the revenue for the HIS should ultimately be found from within existing resources by changing working practices. Some of the more important aspects from a doctor's perspective are discussed below.

The PAS module has improved many clerical functions. The estimated savings are 5 wholetime equivalents at the secretarial and clerical level. All but 1½ of these staff have been re-invested within directorates to take on diagnostic coding.

We carried out pre- and post-implementation assessments for the introduction of ward order entry. The second assessment is made 6 months after implementation and only the results from General Surgery and Urology are available.

For straightforward entries in practised hands there is an undoubted saving of time. Personal order sets are a great help in this respect and help to specify standards across the hospital. The availability of laboratory test results on the system has greatly reduced telephone calls.

Complex drug regimens with frequently changing doses have proved difficult in all hands, although the Intensive Care Unit has adapted remarkably well.

The prescribing of intravenous fluid regimes and the retrieval of what has been given have proved particularly difficult. The Hospital Board decided in January 1990 to suspend this function. The prescribing of intravenous fluids is currently being re-designed and work is about to start on re-designing the retrieval pathway.

Our physicians were particularly sceptical about the added time taken by on line prescribing. They made a special independent study which has shown that on a manual system a junior doctor spends 2.2

min per patient per day on pharmacy-related activities. Prescribing on the computer when they had only recently completed training takes 3.26 min per patient per day. These orders are received directly in Pharmacy and can be dispatched without any other communication. This time is likely to shorten with practice and any slight increase will be more than offset by the ease of ordering laboratory tests.

Administration of drugs by nursing staff has changed fundamentally. The document is clear and only 1 nurse is required to do the drug round. Only those patients prescribed drugs for that particular round need to be visited. The saving in time on drug rounds is 3½ h per week and is likely to increase to up to 14 h when tighter working practices are introduced.

A much higher proportion of patients have proper care plans completed. About 19 h per week are saved on ward handover.

These latter 2 savings have been rightly criticised. The design of care plans was more an academic exercise than a practical one and the intended lightpen choices have been replaced in practice by considerable free text. This is not good use of nursing time. The design and use of care plans is to be reviewed. Admission assessments have also been criticised for being too unwieldy. The lack of a kardex and the poor use of care plans mean there may be less to discuss at handover and the savings may not be a benefit.

To improve user involvement and ownership and to provide a forum for discussion of changes and problems a series of 7 HIS User Groups (HUGS) was established. There is 1 group for doctors, 1 for nurses, etc. These meet monthly and the chairmen of these groups also meet monthly to co-ordinate changes. They ultimately report to the Hospital Mangement Board.

It is difficult to calculate the true cost of this project because of the way the original contract was managed. Subsequent purchasers would not need to repeat much of the basic work and could learn from our mistakes. The capital cost of the HIS system is of the order of £1,000,000 with another £500,000 for the Resource Management and departmental systems. The revenue cost is currently estimated at £560,000 per year.

## The Technology

It is important that the technology should be right. The hardware and the communications to the mainframe, which in our case is housed in the Regional Health Authority, should be robust. The IBM terminals have proved so. We had some problems with lightpens but these seem fewer—they do need cleaning occasionally! The printers need to be fast and the cheaper ones are noisy but allow 2-colour printing. In most areas they need covers to reduce noise. A limited trial of laser printers was very well received in the areas tried, but has so far proved too expensive. The communications to the mainframe have led to unplanned downtime.

This is soluble with appropriate resource and is in the process of being strengthened.

The current version of the software (HC4000) requires routine maintenance and the system has to go down each night for 1 to 2 h. This now takes place at 0300 but still causes problems for emergency admissions and obstetrics. The aim must be to make planned downtime unnecessary, and HC7000 is said to achieve this.

## Discussion

This has been a colossal undertaking and has to be viewed in the wider context of major organisational change. Everyone in the hospital is affected. The importance of local ownership of the system, and the project to introduce it, cannot be over-emphasised. It is important that the right level of investment is made in people as well as the technology, for both are essential for HIS to work successfully. Certainly we feel that anyone following us should invest more resources, both financial and people, into training and support.

If there are problem areas within a hospital, either clinically or managerially, they will be exposed and emphasised by the introduction of HIS. The attitude of the staff on a particular ward has a marked effect on implementation and its success, and can lead to widely differing responses on adjacent wards within the same specialty. It is vital that the management structure within the hospital can cope with and resolve these problems. The Hospital Board feel that this process would have been extremely difficult without the clinical directorate structure. HIS was implemented in 3 years, which is a fast implementation by standards set in the USA, but in a hospital of similar size to ours, could probably be reduced to 2 years.

Whether this system saves time for junior medical staff is still not proven. They are the ones who make most of the transactions. How much their working practices can be altered remains to be seen and this is likely to be influenced by how much consultant staff use the system personally. The absence of an out-patient module in the current software is a disadvantage in this respect.

The turnover of junior staff (and particularly locums) presents a problem for training because it is no longer possible to practise in the hospital without being able to use HIS. New housestaff on the major changeovers in February and August spend the whole of their first day training and a high level of support is available for the first 2 to 3 weeks. Other staff have to be trained as they arrive and this requires good communication between directorates, the personnel department and the HIS team.

The software has, in the main, fulfilled the criteria on which it was chosen but reservations remain about its use for the critically ill patient, particularly the more complex intravenous fluid regimens and some drug prescribing. The loss of the drug chart as a unifying document has been acutely felt in the Medical Directorate, but their experience with it is relatively short.

HIS has produced many benefits for the organisation as a whole and may be essential to survive the financial and demographic pressures of the next few years.

## Acknowledgements

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PAEDIATRIC UROLOGY

# Primary Vesicoureteric Reflux: Treatment with Subureteric Injection of Polytef Paste

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Summary—A series of 34 children with 40 primary refluxing ureters were treated endoscopically with a subureteric injection of polytetrafluoroethylene paste (Polytef). The amount injected ranged between 0.1 and 0.8 ml (mean 0.3). A single injection cured the reflux in 26 ureters (65%) and the grade of reflux improved in a further 9 ureters. Seven ureters required a second injection and reflux was cured in 6 of these. The overall cure rate was therefore 80% after the second injection. There was one complication due to self-limiting ureteric obstruction following injection. The procedure is quick, easy to perform and effective. We have some reservations about the long-term efficiency and safety of subureteric Polytef injection in children.

Primary vesicoureteric reflux (VUR) is common in children. In normal asymptomatic children the incidence is 1%, but 30 to 50% of children with urinary tract infections will have reflux (Smellie and Normand, 1966; Ransley, 1978; Hodson and Cotran, 1982). It occurs predominantly in girls and has a high familial incidence (Jerkins and Noe, 1982). The role of vesicoureteric reflux in the development of chronic pyelonephritis is widely recognised, although the management of VUR remains controversial. There is general agreement that VUR in a non-dilated system can be successfully managed with low dose chemoprophylaxis until the VUR disappears. Severe VUR and recurrent urinary tract infections during antimicrobial treatment are generally taken as indications for surgery (Smellie *et al.*, 1976; International Reflux Study Committee, 1981). Previously, reimplantation operations were all that the surgeon could offer and although ureteric reimplantation is not devoid of complications, it does cure VUR in over 95% of patients. Puri and O'Donnell (1984) published their results using an endoscopic technique for subureteric injection of polytetrafluoroethylene paste (Polytef) in the treatment of reflux—known as the STING procedure. We report our experience using this technique in 40 patients with refluxing ureters. Initially, our aim was to confine the use of this technique to patients with unilateral VUR.

## Patients and Methods

Between February 1987 and September 1989, 34 children with 40 refluxing ureters were treated using the STING technique. There were 28 females and 6 males with a mean age of 7 years 2 months (range 20 months–15 years). There was unilateral reflux in 28 and bilateral reflux in 6 children. The VUR was graded according to the international classification of reflux (International Reflux Study Committee, 1981) (Table).

The STING procedure was performed by 1 surgeon (J.D.A.). The technique described by

**Table** Grade of VUR in 40 Refluxing Ureters in 34 Children Treated with a Submucosal Injection of Teflon

| | *Grade of VUR* | | | | |
|---|---|---|---|---|---|
| | *I* | *II* | *III* | *IV* | *V* |
| No. of ureters | 3 | 10 | 12 | 13 | 2 |

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O'Donnell and Puri (1984, 1986), using the Storz instruments, was used (Fig. 1) and 0.1 to 0.8 ml of Polytef paste were injected (mean 0.3 ml). The children remained in hospital overnight and were discharged the following day. All had an ultrasound scan (USS) of the kidneys and bladder 4 weeks after the procedure to detect any upper tract dilatation, and the Polytef paste was frequently visualised (Fig. 2). A micturating cystogram was performed 3 months after the STING procedure and again the Polytef could often be visualised (Fig. 3). The patients remained on antimicrobial chemoprophylaxis until no reflux could be demonstrated radiologically.

## Results

At micturating cystography 3 months following the STING, VUR was abolished in 26 ureters after a single injection of Polytef (65%) and an improvement in VUR grade was seen in 9 ureters. A single injection failed to improve reflux in 5 ureters. A further 7 ureters were subjected to a second STING procedure with cessation of reflux in 6, giving an overall 80% success rate after 2 injections. Only 1 ureter failed to show any improvement after 2 injections.

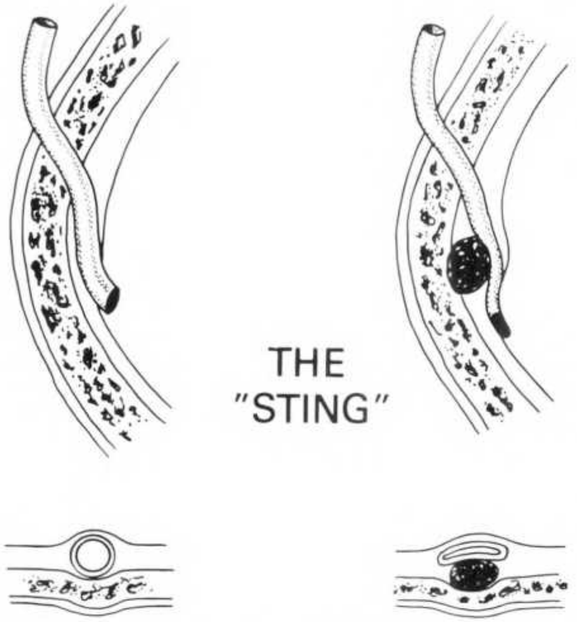

**Fig. 1** Diagrammatic representation of the refluxing ureter before and after Polytef injection. The Polytef supports the intravesical ureter and converts the opening to a crescentic shape.

These patients have been followed up for a mean of 20 months (range 3–36). Those in whom reflux was cured remain well, free from urinary tract infections and do not require antimicrobial drugs. There was 1 complication: an 8-year-old girl developed left loin pain 48 h after the first injection of 0.5 ml Polytef into a Grade II refluxing left ureter and renal USS at that time showed a moderate left hydronephrosis. These symptoms settled quickly without intervention and USS at 1 month was unremarkable. A micturating cystogram at 3 months showed no reflux. No patient showed any sign of ureteric obstruction at USS after 4 weeks.

Six patients underwent reimplantation of the ureters following the Polytef injection. In 2 cases reimplantation followed a failed single injection; in the first of these the VUR (Grade IV) was to a solitary kidney and in the second there was evidence of renal scarring associated with VUR (Grade V). In another patient the unilateral VUR improved from Grade IV to II but was still persistent and reimplantation was therefore performed. In 2 further patients the unilateral VUR improved from Grade IV to II but bilateral VUR was seen on the follow-up micturating cystogram and so the ureters were reimplanted. In the sixth patient subjected to surgery, the VUR improved from Grade IV to II but surgery was then performed; this patient was one of the early patients in the series.

The presence of the Polytef paste and associated

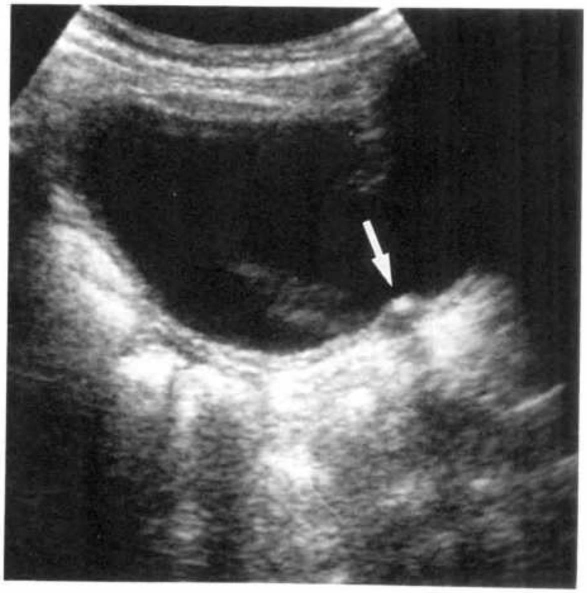

**Fig. 2** Ultrasound scan following the STING procedure. The Polytef paste is clearly seen in the bladder wall.

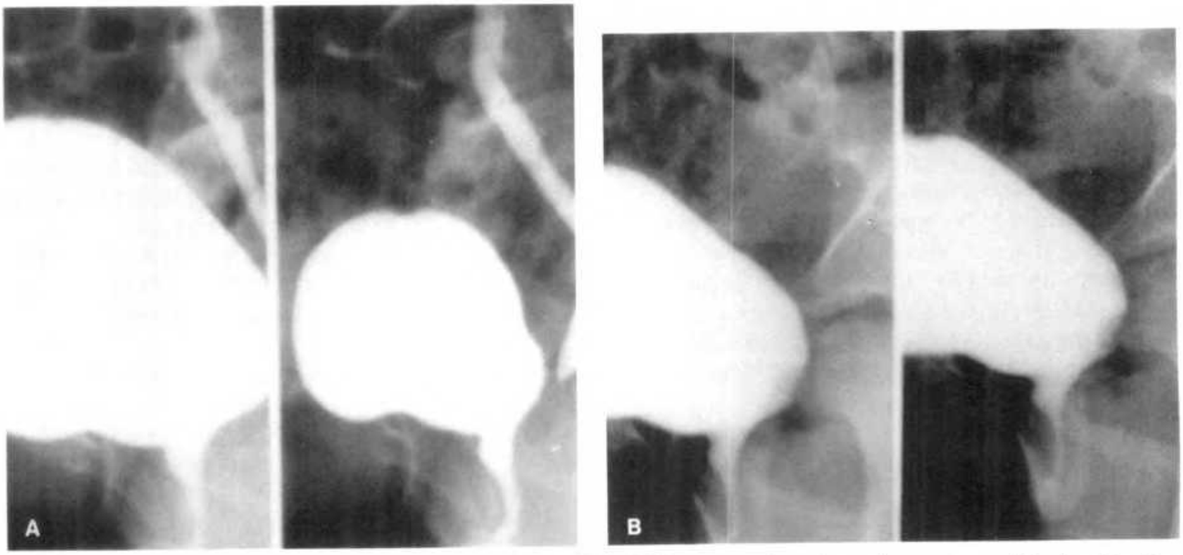

**Fig. 3** (A) Pre-operative micturating cystogram showing left VUR. (B) Post-operative micturating cystogram following injection of 0.3 ml Polytef paste. Reflux is abolished and the Polytef can be visualised.

granuloma did not make reimplantation more difficult. One granuloma was sent for histological examination and this showed a sac containing Polytef granules surrounded by a wall of macrophages and foreign body giant cells (Fig. 4).

## Discussion

Endoscopic subureteric injection of Polytef paste has been used to correct VUR since 1984 and has proved successful in many centres (O'Donnell and Puri, 1986; Kaplan *et al.*, 1987; Puri and O'Donnell, 1987; Schulman *et al.*, 1987). We found the technique simple, effective and safe. It can easily be repeated and does not affect reimplant surgery if this is required. Mastery of the technique requires practice and many of our failures occurred in the first few patients. We had one complication involving mild ureteric obstruction but complications are usually rare (O'Donnell and Puri, 1986;

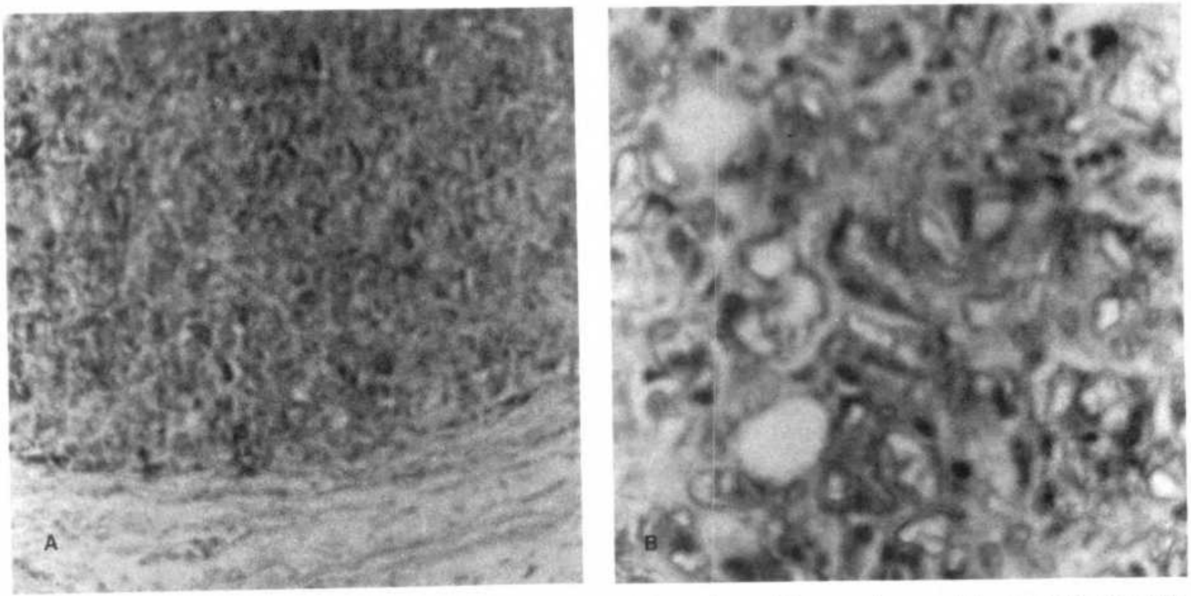

**Fig. 4** (A) Polytef granuloma with capsule (magnification × 50). (B) Granuloma with macrophages and foreign body giant cells. (magnification × 150).

Puri and Guiney, 1986; Kaplan *et al.*, 1987; Schulman *et al.*, 1987). The main problem with the STING technique is the occasional failure, but with experience and attention to detail, success rates of 80 to 90% can be achieved (O'Donnell and Puri, 1986; Kaplan *et al.*, 1987; Schulman *et al.*, 1987). The STING technique has shown impressive results in VUR associated with the neuropathic bladder (Puri and Guiney, 1986; Kaplan *et al.*, 1987), where surgical reimplantation is known to be unrewarding. Although it has not yet achieved the cure rates of reimplant surgery, and its long-term efficacy remains to be demonstrated, the STING technique does have certain advantages. It avoids open surgery, is quick and easy to perform and avoids prolonged hospitalisation. It has been performed as an out-patient procedure (Kaplan *et al.*, 1987) and the economic advantages of this are obvious.

Polytef paste for injection is a sterile injectable paste containing polytetrafluoroethylene that has been pyrolysed, polysorbate and glycerine. Following subureteric injection the paste hardens *in situ* to form a mass which provides a solid support against which the intravesical ureter can anchor and compress (Puri and O'Donnell, 1984). Polytef paste has been used since 1963 for the treatment of deformed vocal cords (Arnold, 1963; Stone and Arnold, 1967) and, since 1974, in the treatment of urinary incontinence (Politano *et al.*, 1974). No untoward side effects have been reported from these applications. Polytef particles are biologically inert but they do elicit a foreign body reaction with giant cells and granuloma (Puri and O'Donnell, 1984; Kaplan *et al.*, 1987; Blake and O'Connell, 1989). USS following STING has shown migration of Teflon particles to the trigone area. Large lobulated granulomata (1 associated with ureteric obstruction) have also been demonstrated on USS (Blake and O'Connell, 1989). Distant migration of Polytef particles following periurethral injection in animals has been reported (Malizia *et al.*, 1984). There is also 1 reported case of Polytef granuloma being found in the lungs of a patient following 2 Polytef injections periurethrally (Mittleman and Maraccini, 1983). His death by suicide was unrelated. Following periurethral injection, particles of Polytef have also been found in regional nodes (Vorstman *et al.*, 1985), but no morbidity has been reported from this. Larger quantities of Polytef (10–20 ml) are injected into a more vascular periurethral area than the small amount (<2 ml) injected behind the ureter, but the long-term effects of Teflon in this situation are not known.

The long-term efficacy of the STING procedure has yet to be established and late recurrence of reflux or delayed ureteric obstruction could occur. More importantly, the long-term safety of Polytef paste injected into children is not known. It is hoped that injection of biocompatible substances such as collagen may overcome the theoretical problems of Polytef.

For these reasons we are cautious in treating bilateral VUR with the STING procedure. We are also a little reluctant to repeat the procedure more than twice, but with the above reservations we believe the STING technique has many advantages when compared with reimplant surgery. It is now firmly established in the treatment of reflux and we look forward to the introduction of the "ideal" substance for this procedure.

## Acknowledgement

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# Ammonia Levels in Paediatric Ureterosigmoidostomy Patients: A Screen for Hyperammonaemia?

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Summary—Hyperammonaemia in the urological patient is a rare and potentially grave condition. It has been reported most frequently in association with ureterosigmoidostomy, where clinical neurological symptoms have developed abruptly in association with markedly elevated plasma ammonia levels. The purpose of this study was to determine whether ureterosigmoidostomy patients might have subclinically elevated plasma ammonia levels, which would put them at risk of subsequently developing hyperammonaemic encephalopathy. Both urine and plasma ammonia levels were assayed in 10 asymptomatic paediatric urological patients with ureterosigmoidostomy. Ten paediatric colocystoplasty patients served as controls. Urine pH and urine ammonia levels were significantly higher in the ureterosigmoidostomy group. There was no significant difference in plasma ammonia levels between ureterosigmoidostomy and colocystoplasty patients. In none of the patients was the plasma ammonia level elevated, but 1 ureterosigmoidostomy patient had an exceedingly high urine ammonia level. It was concluded that an annual serum ammonia level in an asymptomatic ureterosigmoidostomy patient is probably not a valuable screen for subclinical hyperammonaemia.

Hyperammonaemic encephalopathy is usually associated with hepatic dysfunction. It is a rare condition in urological patients but has been recognised with increasing frequency since McDermott's initial report in 1957 of a patient with an ileal pouch, *Proteus* urinary tract infection and hyperammonaemic coma. Among the urological population, ammoniagenic coma has been most frequently reported in ureterosigmoidostomy patients; in the typical case, severe neurological symptoms develop abruptly and without warning. In some of these patients, mild hepatic dysfunction contributed to their encephalopathy. Studies have demonstrated that the bowel is far more absorptive of ammonia than is transitional epithelium and, therefore, those with a ureterosigmoidostomy are at particular risk.

The purpose of this study was to determine whether or not healthy, asymptomatic paediatric patients with ureterosigmoidostomy had subclinically elevated plasma ammonia levels which put them at risk of developing hyperammonaemic encephalopathy. Because of the absorptive capacity of bowel for ammonia, 10 asymptomatic colocystoplasty patients were also studied as a control group.

## Patients and Methods

We evaluated 20 paediatric urological patients with either ureterosigmoidostomy (10) or colocystoplasty (10). All were managed at the Institute of Urology, London, and were under the long-term care of one of us (P.G.R.). The patients ranged in age from 8 to 18 years and were all clinically well. In order to assess renal function, plasma urea and creatinine were measured. Hepatic function was assessed by measuring plasma aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase and total bilirubin. To determine the presence of a urea splitting organism, all patients underwent urine culture and measurement of urine pH. Finally,

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ammonia levels were measured in each patient's urine and plasma.

Plasma ammonia was measured spectrophotometrically using a glutamate dehydrogenase-based enzymatic procedure (Boehringer Mannheim GmBH, Kit no. 125851), while urine ammonia was estimated colorimetrically using the Berthelot phenol/hypochlorite procedure.

EDTA plasma was used from blood collected into chilled ammonia-free tubes and transported on ice to the laboratory for immediate centrifugation and analysis. For the urine assays, spot specimens were collected and either analysed immediately or stored at −20°C until assayed. All plasma and urine assays were performed in duplicate.

## Statistical Analysis

Urine pH and plasma ammonia levels were compared in the 2 surgical groups with the 2-sample *t* test. The Mann Whitney test was used to compare urine ammonia levels in the 2 groups.

## Results

The results are summarised in the Table. They demonstrate that urine pH was significantly higher in the ureterosigmoidostomy than in the colocystoplasty group. Spot urine ammonia levels were also significantly higher in the ureterosigmoidostomy patients. Plasma ammonia levels were not significantly different between the 2 groups.

All 20 patients had normal renal function, assessed in terms of plasma urea and creatinine. In addition, all 20 had normal liver function studies, assessed in terms of AST, ALT, alkaline phosphatase and total bilirubin.

All of the ureterosigmoidostomy patients had urine cultures positive for *Escherichia coli*. Only 2 of the 10 colocystoplasty patients had positive urine cultures, 1 with *Proteus* and 1 with a coliform infection. The patient with *Proteus* urinary tract infection had the highest urine pH (8.7) and urine ammonia (74 mmol/l) in his group, but his serum ammonia was within the normal range (42 µmol/l).

**Table** Results

| | *Ureterosigmoidostomy Mean (range)* | *Colocystoplasty Mean (range)* |
|---|---|---|
| Urine pH | 8.3 (7.1−9.3)* | 7.5 (6.0−8.7) |
| Urine ammonia (mmol/l) | 101 (21–542)† | 26 (5–74) |
| Plasma ammonia‡ (µmol/l) | 35 (22–51) NS | 34 (27–44) |

* ($P<0.03$) Two-sample *t* test.
† ($P<0.02$) Mann Whitney test.
‡ normal plasma ammonia: 15–55 µmol/l (male), 11–48 µmol/l (female)
NS = not significant.

Of note is the fact that no patient in either group had a plasma ammonia level which exceeded the upper limits of normal for the method used. However, the patient with the highest plasma ammonia level (51 µmol/l; upper limit of normal 55 µmol/l) was of particular interest. He was a ureterosigmoidostomy patient with the highest urine pH (9.3) and the highest urine ammonia level (542 mmol/l) of all the patients studied. If any patient seemed at risk of developing hyperammonaemia it was this young man, who was instructed to empty his colon with greater frequency.

## Discussion

The 2 sources of plasma ammonia in man are the intracellular catabolism of amino acids and muscle adenine, and a small fraction from the action of enzymes and bacteria on bowel contents. Plasma ammonia is then metabolised by 1 of 2 mechanisms: ammonia may combine with glutamic acid to form glutamine (in a detoxification process) or the ammonia that reaches the liver enters the Krebs-urea cycle to be converted to urea. Urea is then excreted by the kidneys (Podolsky and Isselbacher, 1987) (Fig. 1).

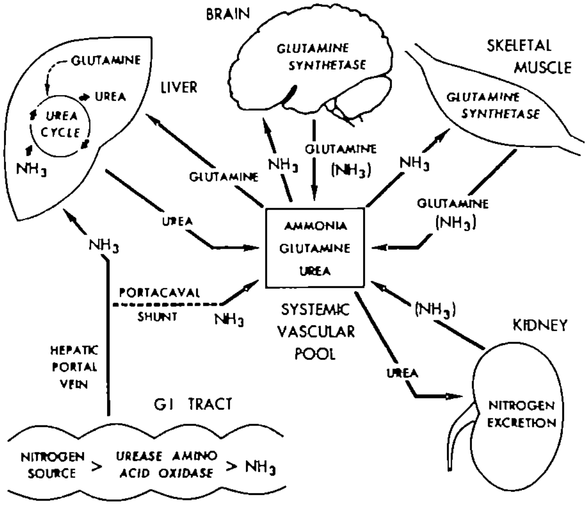

**Fig. 1** Human ammonia metabolism. Reproduced from the *Journal of Clinical Investigation* (1979), **63**, pp. 449–460 by copyright permission of the American Society for Clinical Investigation.

Ammoniagenic coma is usually associated with altered hepatic metabolism of ammonia. Thus patients with liver disease, an acquired or congenital deficiency of hepatic enzymes of the Krebs-urea cycle, Reye's syndrome or portocaval shunts are at particular risk. Ammoniagenic coma is a rare finding in the absence of liver disease (Konn and Atterbury, 1987).

The first description of ammoniagenic coma occurring in a urological patient was by McDermott in 1957. The patient was an 8-year-old boy with an ileal pouch which was created because of urinary incontinence due to bladder neck operations for the treatment of posterior urethral valves. He was admitted in a deep coma with both a *Proteus* pyelonephritis and hepatitis, and a markedly elevated serum ammonia level (113 µmol/l). He responded rapidly to antibiotics and fluid and electrolyte therapy.

Since McDermott's case report, 11 additional urological patients have presented with ammoniagenic coma, with plasma levels ranging from 65 µmol/l in a paediatric patient to 373 µmol/l in an adult. Four patients had a ureterosigmoidostomy, 2 of them with abnormal liver function (Silberman, 1958; Mortensen *et al.*, 1972; Mounger and Branson, 1972; Kaufman, 1984). Only 7 were paediatric patients—5 with prune belly syndrome, 1 with an obstructing ectopic ureterocele and 1 with a neurogenic bladder and bladder calculi (Kuntze *et al.*, 1985; Samtoy and De Beukelaer, 1980; Drayna *et al.*, 1981; Ullman *et al.*, 1981; Sinha and Gonzalez, 1984; Diamond *et al.*, 1989). All 7 paediatric patients had urinary tract infection with urea splitting organisms and all had normal liver function. Thus urological patients developing ammoniagenic coma have fallen into 2 broad categories: those with ureterosigmoidostomy and those with massively dilated urinary tracts and infection with a urea splitting organism. Why should these patients be at risk of developing ammoniagenic coma?

In solution, ammonia exists in equilibrium as the ammonium ion (NH4+) or the free base (NH3). At a urine pH of 7.4, only 1% of ammonia molecules exist as NH3, but at a urine pH of 9, 50% of the molecules exist as NH3 (Samtoy and De Beukelaer, 1980). An alkaline urine results when urea splitting organisms infect the urinary tract or predominate among colonic flora in ureterosigmoidostomy patients. The free base (NH3) is lipid soluble and rapidly permeates all cell membranes, in contrast to the charged ammonium ion (NH4+). As the ammonia molecule diffuses from the alkaline urinary tract into the bloodstream, it is converted to the poorly permeable ammonium ion (NH4+) in a process known as "diffusion trapping" (Orloff and Berliner, 1958). This results in an elevated peripheral blood ammonia level.

In all 7 paediatric urological patients with ammoniagenic coma there was urinary infection with a urea splitting organism resulting in a massive generation of ammonia and an alkaline urine. There was also a massively dilated collecting system, producing an increased surface area through which ammonia could be absorbed.

With ureterosigmoidostomy, there is diversion of the urinary stream into the colon which provides an abundance of urea that is converted to ammonia (NH3) by urea splitting organisms (Fig. 2). The colon is far more absorptive of ammonia than transitional epithelium, putting these patients at greater risk of hyperammonaemia (Boyce and Vest, 1952). In addition, stasis of urine within the colon would enhance ammonia absorption. For these

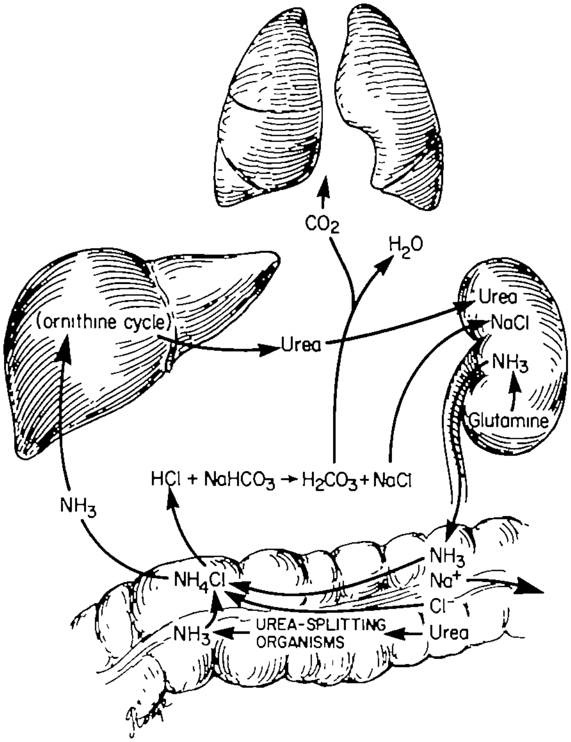

**Fig. 2** Diagram of ammonia-urea cycle in ureterosigmoidostomy. Ammonia (NH3) is liberated by urea splitting organisms in colon and is also excreted into colon by kidneys. Reprinted with permission from the Williams and Wilkins Company. Kaufman, J. J. (1984). Ammoniagenic coma following ureterosigmoidostomy. J. Urol., **131**, 743–745.

reasons, patients with ureterosigmoidostomy seemed at particular risk of developing hyperammonaemia.

The urological patients who presented with hyperammonaemic coma were asymptomatic until neurological symptoms arose secondary to ammonia toxicity. We wondered if screening plasma ammonia levels in patients at risk might reveal individuals with subclinical hyperammonaemia.

This study has demonstrated that in a small group of healthy paediatric ureterosigmoidostomy patients, plasma ammonia levels were within the normal range but urine ammonia levels and urine pH were elevated. The most intriguing results were from the ureterosigmoidostomy patient with the highest plasma ammonia (51 μmol/l). This patient had by far the highest urine ammonia level (542 mmol/l). This raises the possibility that urine ammonia levels may be an earlier predictor of hyperammonaemia. While the normal 24-h urinary excretion of ammonia is well documented at 25 to 60 mmol, a normal range of spot urine levels has not been established.

On the basis of this study we are unable to conclude that an interval plasma ammonia level is a valid screening test for hyperammonaemia in asymptomatic ureterosigmoidostomy patients. However, if neurological symptoms develop in patients with ureterosigmoidostomy a plasma ammonia level should be obtained immediately, although this test is not always locally available.

## Acknowledgement

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# Catheter-less Suprapubic Cystolithotomy in Children

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Summary—Bladder stones in children are common in developing countries and the procedure of choice for their removal is suprapubic cystolithotomy. It is standard practice to drain the bladder for a few days post-operatively to prevent urinary leakage. We have observed that, if the bladder is closed meticulously in 2 layers, bladder drainage by means of a catheter is not required. We have analysed 86 children treated by suprapubic cystolithotomy without a catheter. Size of the stones and intra-operative findings were noted and it was found that 85% of the patients had an excellent result; 10% had a satisfactory result and 4.7% were unsatisfactory. The advantages of the procedure and selection of the patients are discussed.

Although bladder stones in adults can be removed by various endoscopic procedures, suprapubic cystolithotomy remains the procedure of choice in children. This is mainly due to the small size of the urethra, which is unable to accommodate the larger instruments used for endoscopic manipulation. The standard practice has been to drain the bladder for a few days after the operation (Blandy, 1986; Newsam, 1987) to prevent urinary leakage. We have observed that, if the bladder is closed meticulously, catheter drainage is not required. We have studied 86 children treated by catheter-less suprapubic cystolithotomy in this department over the last 8 years.

## Patients and Methods

The study group comprised 86 children presenting with vesical calculi. There were 47 boys and 39 girls, the youngest being a 1-year-old boy and the eldest a 12-year-old girl (Table 1).

In addition to other urological investigations, cystoscopy was carried out just before the operation in order to exclude bladder outlet obstruction, to confirm the presence of stone and to inspect the rest of the bladder for associated pathology. Patients with outlet obstruction were omitted from the study.

In all cases a transverse suprapubic skin incision was made and the bladder was opened vertically, with bladder wall thickness and mucosal oedema being noted. After removal of the stone, the bladder was closed in 2 layers using fine absorbable sutures-inner mucosal continuous and outer muscle interrupted. The bladder closure was confirmed as leak-proof (only in the initial stage of the study) by passing a urethral catheter, distending the bladder to a pressure of 60 cm of water and then immediately removing the catheter. A retropubic corrugated rubber drain was used in all cases.

The number and size of the stones were measured. Of 86 patients, 8 had 2 stones and 1 had 3 stones; the remainder had a solitary stone (Table 2).

Each child was made ambulatory a few hours post-operatively and the drain was removed a mean of 48 h later, when the patient was discharged from hospital. However, most of the children were completely ambulatory within 8 to 10 h of surgery

**Table 1** Age Distribution

| *Age group (years)* | *No. of patients* | *%* |
|---|---|---|
| 1–3 | 15 | 17 |
| 3–6 | 41 | 48 |
| 6–9 | 18 | 21 |
| 9–12 | 12 | 14 |

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**Table 2** Stone Sizes in Patients with Solitary Stones

| *Stone size (cm)* | *No. of patients* | *%* |
|---|---|---|
| <1 | 14 | 18 |
| 1.1–2 | 29 | 38 |
| 2.1–3 | 22 | 29 |
| >3 | 12 | 16 |

and were fit to be discharged at that stage. Those who developed complications required a longer stay in hospital.

## Results

A total of 73 patients (85%) passed urine well and made a smooth recovery.

Nine patients (10%) were unable to pass urine and were catheterised. There was no evidence of a suprapubic leak and the catheter was kept in place for 5 days, after which time they passed urine with a good stream. Of these 9 patients, 4 were boys and 5 were girls. In 7 cases the stones measured 2 to 3 cm and in 2 cases they exceeded 3 cm. Three patients had red, inflamed and oedematous bladder mucosa and 1 had a superficial wound infection.

Two patients were able to pass urine but had significant urinary leakage from the drain. This stopped after passing a catheter *per urethram* which was kept in place for 5 days. Both patients were boys whose stones were larger than 3 cm. One had a thick bladder wall and inflamed, oedematous mucosa and the other had a wound infection.

A 4½-year-old boy with 2 stones measuring 2.5 cm and a thick, hypertrophied bladder was able to pass urine but had significant urinary leakage from the main wound, probably due to blockage of the corrugated drain. He was catheterised and the catheter was kept *in situ* for 7 days. The leak stopped but he then developed a wound infection.

A 5-year-old boy had a single stone larger than 3 cm, a thick bladder wall and inflamed red mucosa. After the operation he was able to pass urine and there was no leakage from the drain. On the second day he developed cellulitis of the skin around the wound; a urethral catheter was passed but the cellulitis increased and he became feverish. On the fourth post-operative day, following insertion of a suprapubic catheter and drainage of the perivesical area, his condition improved. The suprapubic catheter was removed after 10 days, by which time he was passing urine well.

Superficial wound infection was seen in 4 of the 86 patients but none required secondary suturing.

## Discussion

The incidence of endemic bladder stones in the Western world is markedly reduced as a result of the overall improved quality of life, but the incidence is still relatively high in developing and underdeveloped countries (Drach, 1986). Many endoscopic procedures for crushing and removing bladder calculi are not feasible in children because of their narrow urethra and so suprapubic cystolithotomy is the treatment of choice. Blandy (1986) and Newsam (1987) have recommended draining the bladder for a few days to prevent urinary leakage.

Catheterisation has many disadvantages. Children do not tolerate it well as they get frequent bladder spasms. Being small in size, the catheter does not drain urine freely. There are potential hazards following catheterisation, such as infection, stricture, etc. In view of these disadvantages, we decided to use catheter-less procedures.

It is well known that in children, intravesical pressure during micturition does not usually exceed 60 cm of water (Whitfield, 1985). After removal of the stone the bladder is closed in 2 layers. Even when the bladder was distended to a pressure of 60 cm $H_2O$, there was no leakage from the suture line. We therefore deduced that a properly closed bladder should withstand the micturation pressure and it would not be necessary to use a catheter to prevent urinary leakage.

Of the 86 patients, 73 (85%) had a good urinary stream, made an uneventful recovery and were discharged early from hospital; this was considered an excellent result. Nine patients required only urethral catheterisation for a variable period but otherwise made a good recovery; this was considered a satisfactory result.

Only 4 patients had an unsatisfactory result. They developed a significant urinary leak either from the drain or from the main wound, resulting in either wound infection or, in 1 case, re-exploration. Of these 4 patients, 3 had a stone measuring more than 3 cm, a thick bladder wall and red, oedematous bladder mucosa. In such cases this procedure may not be suitable. In the remainder, however, reduced morbidity and hospital stay were gratifying results of this procedure. We concluded that an essential step in the operation was meticulous closure of the bladder with accurate placement of the drain. If a stone was excessively large and the bladder wall was thick and hypertrophied with inflamed mucosa, then catheterisation was necessary. In properly selected patients, catheter-less suprapubic cystolithotomy is a safe procedure with considerably less morbidity and reduced hospital stay.

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# Case Reports

## Malignant Phaeochromocytoma of the Bladder—Active or Inactive

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### Case Report

R.D., a 52-year-old Caucasian male, presented with a 10-month history of frequency, dysuria and haematuria. He had a history of hypertension, controlled on enalapril, but no recent history of post-micturition headaches, syncope, sweating or palpitations.

Cystoscopy revealed an 8-cm tumour on the bladder dome and despite bladder distension, biopsy and transurethral diathermy there were no systemic haemodynamic changes. Microscopy and positive staining with neuron specific enolase identified the tumour as a paraganglioma (phaeochromocytoma). The diagnosis of a hormonally active phaeochromocytoma was considered unlikely in view of the tumour's behaviour at cystoscopy and catecholamine estimations, which revealed a serum noradrenaline level of 4.7 nmol/l (0.1–6.3) and a serum adrenaline of 0 nmol/l (0–1.5). Laparotomy with a view to partial cystectomy was performed after a CT scan revealed no evidence of extravesical spread. At laparotomy multiple metastatic deposits were found within the peritoneal cavity. With handling of the main tumour there was a sudden increase in blood pressure to 280/210 and urgent alpha blockade was instituted; 1 mg phentolamine intravenously led to a precipitous fall in blood pressure to 70 systolic which stabilised with fluid resuscitation. The partial cystectomy and ileal patch augmentation cystoplasty were completed and histopathology revealed invasion of muscularis (Fig. 1), blood vessels and peritoneum (Fig. 2).

### Comment

Phaeochromocytomas of the urinary bladder are thought to arise in the paraganglia of the viscero-autonomic nervous system, located submucosally either in the dome or in the posterior wall close to the trigone (Melicow, 1977). It is an uncommon lesion, accounting for less than 1% of all phaeochromocytomas (Melicow, 1977) and 0.06% of all bladder tumours (Salo *et al.*, 1989). Of all bladder phaeochromocytomas, 10 to 15% are malignant and 83% are hormonally active (Salo *et al.*, 1989). The usual presenting features include hypertension, haematuria and post-micturition syncope, headaches, sweating or palpitations.

In this case we demonstrate the dangers of making the diagnosis of a non-functioning phaeochromocytoma. The absence of haemodynamic

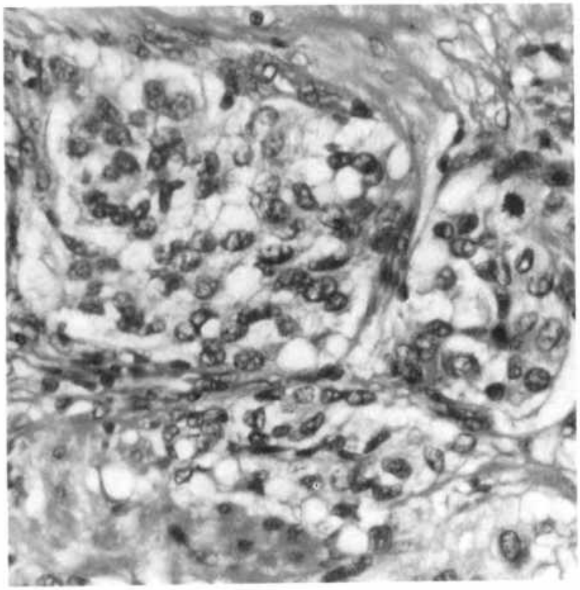

**Fig. 1** Phaeochromocytoma infiltrating the muscularis of the bladder. (H and E × 66).

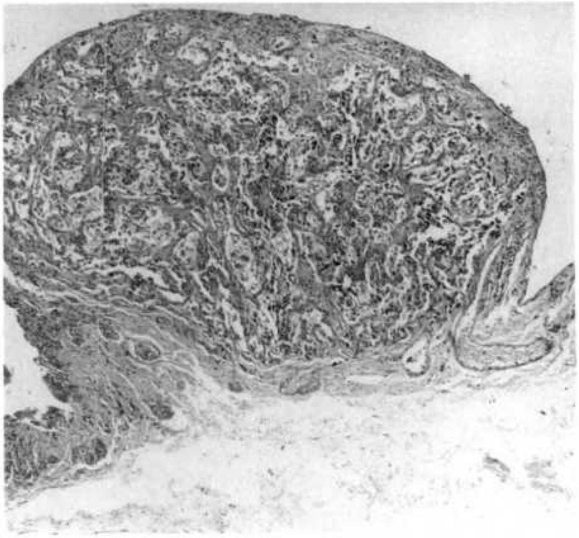

**Fig. 2** Metastatic phaeochromocytoma in peritoneum. (H and E × 13.2).

changes with limited endoscopic manipulation and normal serum catecholamine levels do not exclude the diagnosis of a hormonally active tumour. It has been show that the tumour's secretory activity is limited to a short spike during bladder contraction (Messerli *et al.*, 1982) and that the levels fall to within normal limits 5 min. after voiding. It is therefore not surprising that the resting plasma catecholamine levels were within normal limits in our case; 24-h urinary catecholamine determinations, although not performed in this case, are usually normal, indicating that the total amount of secreted catecholamines is small (Messerli *et al.*, 1982).

We recommend that all bladder phaeochromocytomas are treated as potentially active irrespective of the clinical presentation or serum catecholamine levels. In this way elective adrenergic blockade can be introduced pre-operatively to avoid major blood pressure fluctuations.

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# Xanthogranulomatous Pyelonephritis and Ureterocutaneous Fistula

N. WARNOCK, K. J. O'FLYNN and D. G. THOMAS,
*Departments of Urology and Radiology, Lodge Moor Hospital, Sheffield*

## Case Report

A 44-year-old man with complete tetraplegia (C5) following a road traffic accident 6 years previously was admitted with a 2-year history of a recurrent abscess on the anteromedial aspect of the left thigh. A sinogram showed a tubular network of cavities extending to the level of L4 (Fig. 1). In addition, the left ureter filled with contrast at an early stage, revealing a radiolucent intraluminal filling defect confirmed by retrograde ureterography (Fig. 2). Small calcified stones were seen in the kidney. An IVU showed no function in the left kidney. At operation the left ureter contained an impacted stone (corresponding to the filling defect) and communicated with the psoas abscess. The kidney was small and scarred and nephroureterectomy was performed. Histology of the resected specimen showed features of xanthogranulomatous pyelonephritis. Staining with thioflavine T indicated the presence of amyloid.

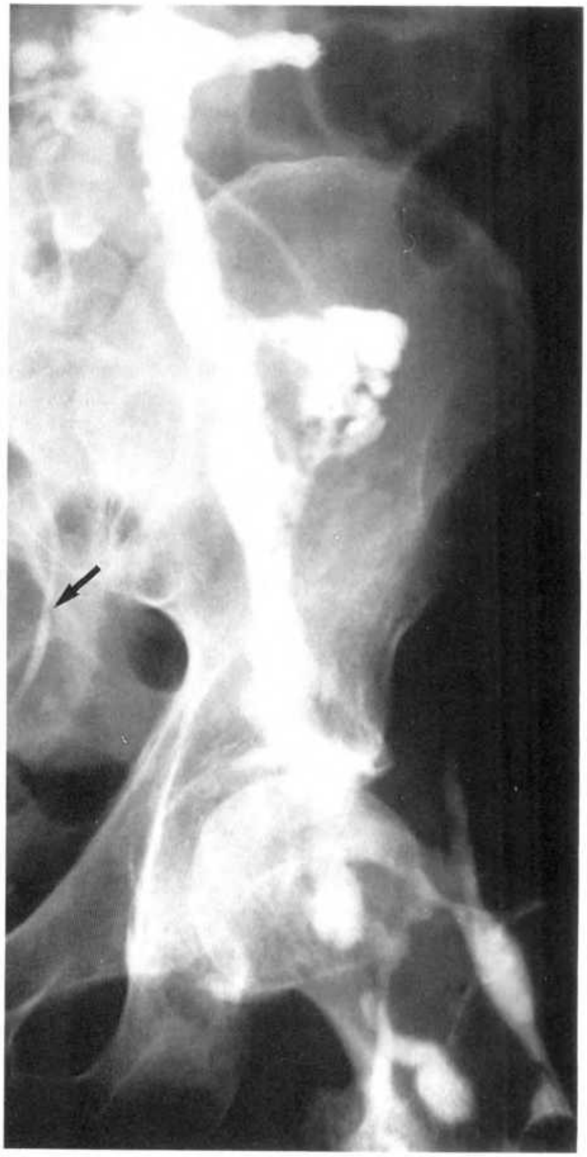

**Fig. 1** Sinogram shows a psoas abscess communicating with the ureter (arrow).

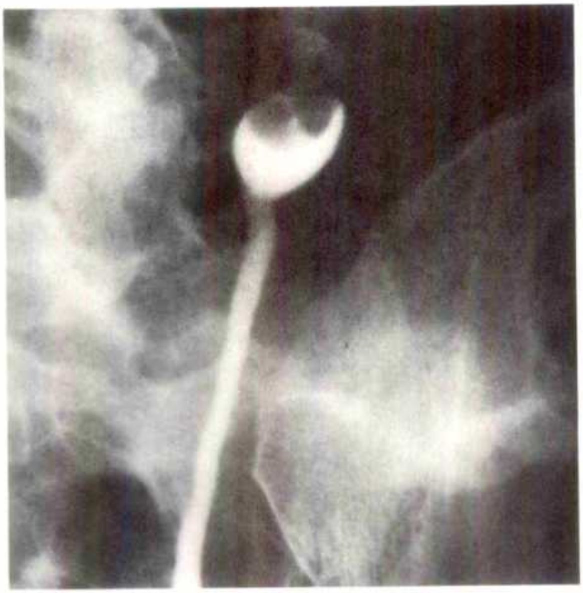

**Fig. 2** Retrograde ureterogram confirms a large intraluminal filling defect.

## Comment

Xanthogranulomatous pyelonephritis (XPN) is a chronic renal parenchymal infection characterised by tissue necrosis and phagocytosis of liberated cholesterol and other lipids by macrophages (xanthoma cells). Recognised aetiological factors include calculus disease, obstructive uropathy, recurrent urinary tract infections and prolonged paralysis (Tolia *et al.*, 1980). Fistula and sinus formation, while rare in XPN, are well documented and total nephrectomy with primary excision of the fistula or sinus (if practicable) is the treatment of choice (Parsons *et al.*, 1986). XPN in association with ureterocutaneous fistula has not previously been described in the English literature. Chronic infections commonly result in amyloid deposition, although the patient had no evidence of secondary systemic amyloidosis.

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# Obstructive Jaundice due to Arteriovenous Fistula after Right Nephrectomy

S. R. ALVAREZ, A. G. RUIZ, R. P. SANCHEZ and R. O. DE DIEGO, *Department of Surgery and Department of Medicine, Gastroenterology Division, Section Red Cross Hospital, Torrelavega, and National Hospital Valdecilla, Santander, Spain*

## Case Report

A 69-year-old woman presented as an emergency with colicky abdominal pain. She had undergone right nephrectomy due to renal tuberculosis 30 years previously. For the last 3 years she had suffered from repeated attacks of biliary colic, some of which were accompanied by transient jaundice and bilirubinuria.

On examination her blood pressure was 160/90 mmHg; she was slightly icteric and tender in the right hypochondrium. Biochemical analysis revealed normal SGOT, SGPT and alkaline phosphatase, gamma GT 204 u/l, with a total bilirubin of 2.4 mg/100 ml and a direct bilirubin of 1.9 mg/100 ml.

Plain abdominal X-ray (Fig. 1) showed a calcified nodular mass in the right hypochondrium. Ultrasonography revealed multiple stones in the gallbladder. The common bile duct measured 10 mm in diameter and contained a defect, possibly caused by a stone.

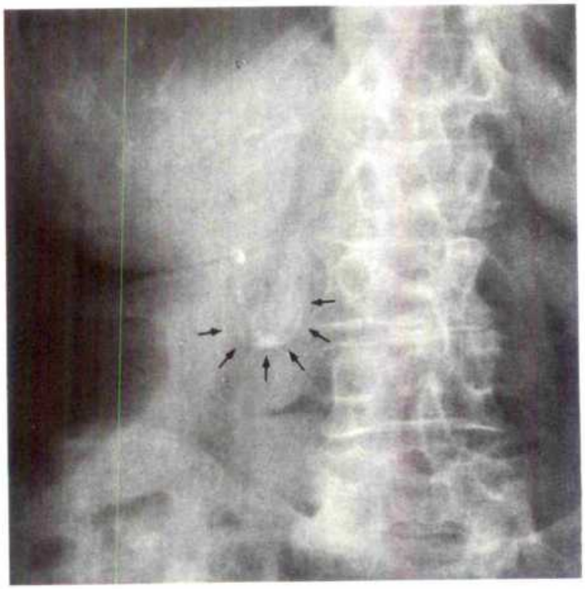

**Fig. 1** Calcified nodular mass in the right hipochrondrium (Arrows).

Her symptoms disappeared on conservative treatment and blood pressure fell to 130/90 mm Hg.

At elective surgery on the seventh day the gallbladder was found to be atrophied and no stones were felt within it.

The common bile duct appeared swollen and displaced towards the midline. An aneurysmal swelling was observed at the apex of the vascular stump of the previous right nephrectomy with calcification of its walls. Cholecystectomy and per-operative transcystic cholangiography showed a dilated biliary tract with displacement towards the midline and a filling defect at the level of the middle third (Fig. 2). This proved to be an arteriovenous fistula of the vascular stump of the right nephrectomy.

The origin of the renal artery was clamped and the renal vein was clamped at its entry to the cava. The fistula and aneurysmal zone were reresected with closure of the new stumps with a continuous monofilament suture.

Further cholangiography showed the disappearance of both the defects within the bile duct and the extrinsic compression.

The post-operative course was uneventful. Histological examination showed chronic cholecystitis and an arteriovenous fistula. In the arterial zone of the fistula there were lipoid deposits with calcific encrustations and proliferation of the intima.

## Comment

This is the first report of a patient with obstructive jaundice secondary to compression of the bile duct by aneurysmal enlargement of the vascular stumps of the right renal pedicle due to formation of an arteriovenous fistula (Morin *et al.*, 1986), although nephrectomy with mass ligature of the pedicle is a recognised cause of arteriovenous fistula (Joyex *et al.*, 1984; Feldman *et al.*, 1985).

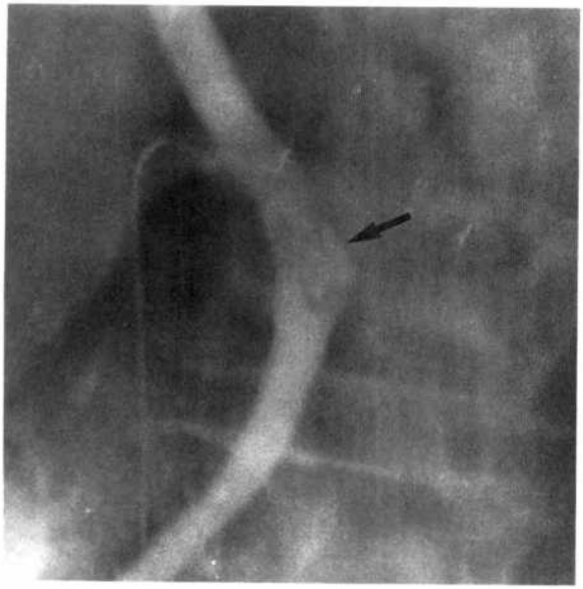

**Fig. 2** Cholangiography: dilated biliary tract with displacement towards the midline and a filling defect on the middle third (Arrow).

Abdominal auscultation was not carried out prior to surgery and this might have revealed an abdominal murmur since a murmur was audible when the abdomen was opened. The diagnosis was also made difficult by calcification inside the aneurysm which confused it echographically with the gallbladder.

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# Bilateral Ureteric Strictures Secondary to Candidiasis

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## Case Report

A 42-year-old housewife with diabetes mellitus presented with a 1-week history of fever and loin pain. Ultrasonography revealed bilateral hydronephrosis and hydroureters.

A right antegrade nephrostogram disclosed a dilated pelvicaliceal and ureteric system down to the level of the sacroiliac joint. A left antegrade nephrostogram showed a dilated collecting system with 2 ureteric narrowings, 1 at the junction of the upper and middle third and the other near the vesicoureteric junction.

Cystoscopy was performed and a double pigtail stent inserted in the left ureter. There was difficulty in manipulating the double pigtail stent into the right ureter and this was complicated by a ureteric perforation.

At laparotomy a 2-mm perforation was noted on the anterior aspect of the right ureter below the stenosis. The ureter was repaired and a double pigtail stent placed. Histopathology of the periureteric tissue revealed necrotic tissue and inflammatory granulation with large numbers of spores and hyphae of *Candida albicans*. Urine and blood cultures grew *Candida albicans*. Urine cultures for tuberculous bacilli were negative. Intravenous amphotericin was given for 4 weeks.

One month after completion of treatment both double pigtail stents were removed. A retrograde pyelogram showed a dilated right collecting system with no narrowing. The left side was similarly dilated but there were 2 strictures as earlier described (Fig.). Repeat urine cultures were negative for fungus.

## Comment

This patient with renal and systemic candidiasis developed multiple stenoses of both ureters. Although obstructive uropathy secondary to candidiasis can be due to fungus balls and necrotic papillae (Knepshield *et al.*, 1968; Raphael and Badgery, 1985), Cohen (1973) reported a case of ureteric candidiasis which resolved after treatment. In our patient, however, the 2 narrowings in the left ureter persisted despite adequate treatment. We believe this to be secondary to post-inflammatory fibrosis. As far as we know, there is no reported case of strictures secondary to renal tract candidiasis. Thus renal tract candidiasis should be considered a potential (albeit rare) cause of strictures of the ureters.

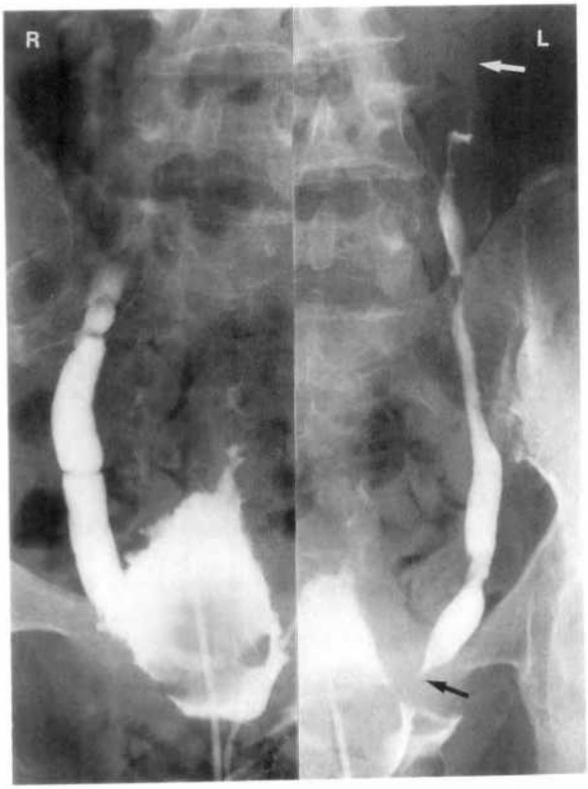

**Fig.** Retrograde pyelogram shows 2 strictures of the left ureter (Arrows).

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# Detrusor Instability Following Colchicine Therapy

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Detrusor instability may occur secondary to bladder outflow obstruction or neurological disorders (when it is defined as detrusor hyper-reflexia) but is often idiopathic. We report a case in which detrusor instability and increased gastro-intestinal motility occurred synchronously after commencing colchicine therapy.

## Case Report

A 47-year-old woman with a 5-year history of scleroderma affecting the left arm was treated with colchicine 500 mg *tds*. One month after commencing this treatment she developed urinary frequency and urgency, stress incontinence, dyspepsia, frequent defaecation and abdominal pain. She was otherwise well and had no previous history of these symptoms prior to colchicine therapy. Apart from cutaneous scleroderma, examination revealed no abnormality and there was no evidence of neurological deficit. Medium-fill videocystometrography demonstrated systolic detrusor instability with a maximum filling detrusor pressure of 21 cm $H_2O$ and a bladder capacity of 240 ml (Fig.). On coughing stress incontinence was demonstrated and this appeared to be secondary to opening of the bladder neck with unstable detrusor

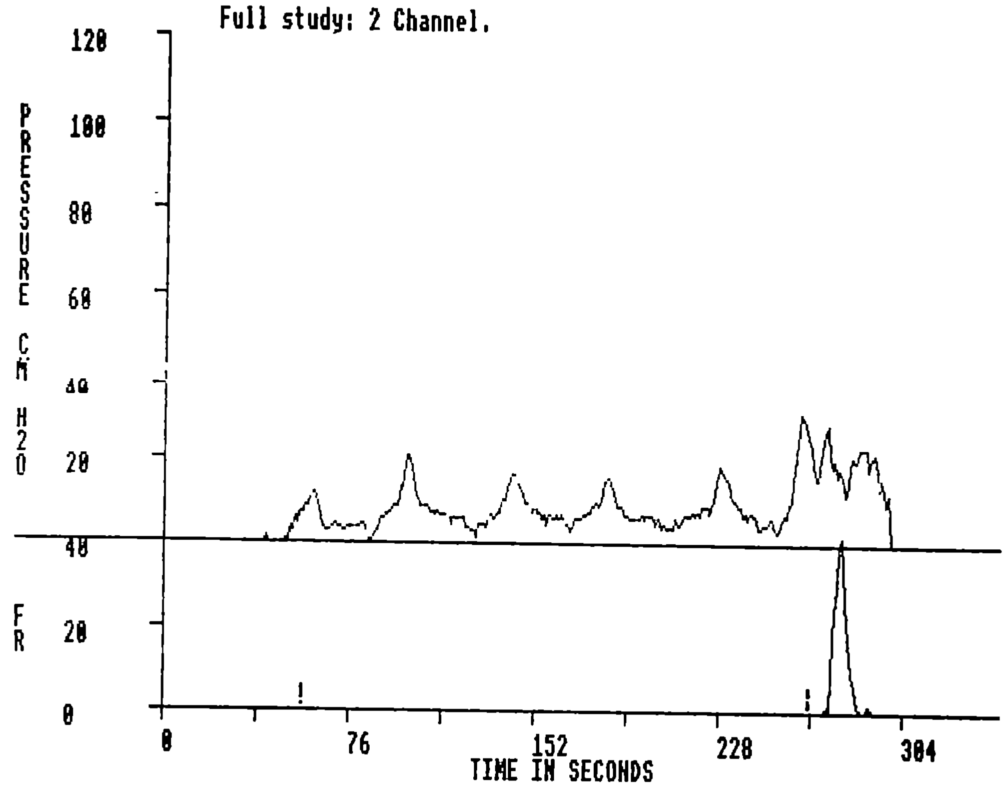

**Fig.** Urodynamic study showing "systolic" detrusor instability and rapid unobstructed voiding

contractions. She voided rapidly and to completion with a maximum voiding pressure of 32 cm $H_2O$ and a maximum flow rate of 42 ml/s (Fig.). Treatment with terodiline 25 mg *bd* was commenced with some symptomatic relief and urodynamic evidence of improvement, although this was discontinued after 3 months due to dizziness. Gastro-intestinal side effects worsened over 6 months and colchicine therapy was therefore discontinued but urinary frequency and urgency persisted.

## Comment

The aetiology of primary detrusor instability is not known, although it has been suggested that it might be due to depletion of VIP-positive nerve fibres or reduction in cholinergic nerve fibre density (Mundy, 1988). Peripheral neuropathy has been described after colchicine therapy, particular after excessive dosage, and this is thought to be due to binding of the drug to tubulin leading to impairment of axoplasmic transport (Riggs *et al.*, 1986). Colchicine may also cause myopathy directly by damage to lysosomes and myofilaments in muscle (Kontos, 1962; Kuncl *et al.*, 1987).

The bladder is very rarely involved in scleroderma and the few cases described have been shown to have fibrosis of the bladder wall leading to hypocompliance on filling and restriction of the bladder capacity (Lally *et al.*, 1985). The urodynamic findings in this case are not typical of scleroderma of the bladder. The synchronous occurrence of systolic detrusor instability and symptoms of increased gastro-intestinal motility after the commencement of colchicine therapy in this case could be attributed to peripheral autonomic neuropathy, which is a recognised side effect of this drug. Detrusor myopathy causes hypocontractility and this is therefore unlikely to be a side effect of colchicine in this case. The persistence of urinary symptoms after discontinuation of colchicine therapy indicates the possibility of irreversible nerve damage.

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# Ureteric Valves in an Ectopic Ureter Associated with Renal Dysplasia

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True valves in the ureter are very rare. About 30 cases have been published in the English literature (Sant *et al.*, 1985).

Most cases are associated with other congenital urological malformations and are not suspected before operation or autopsy. We report a case in which the valves existed in an ectopic ureter discharging into the seminal vesicle. We were unable to find any other reported case.

## Case Report

A 27-year-old man was admitted with left renal colic. Clinical examination, including palpation of the scrotal contents, revealed no abnormalities. Ultrasonic examination of the abdomen failed to demonstrate renal tissue on the left side. The right kidney was large but otherwise normal. Behind the bladder, multiple small cystic structures were seen (Fig. 1).

A computed tomographic scan of the abdomen and pelvis also failed to identify a left kidney. A large polycystic mass was seen behind the bladder. At cystoscopy, no orifice was identified on the left side.

The mass was explored through a Pfannenstiel incision and was found to be a cystically dilated seminal vesicle. A dilated ureter entered this seminal vesicle. The ureter was followed proximally through a second, pararectal incision. It led to a very small kidney. The seminal vesicle, ureter and kidney were removed *en bloc*.

Pathological examination showed several valves in the dilated portion of the terminal ureter (Fig. 2). Microscopically these valves contained the 3 layers of the ureter: epithelium, lamina propria and smooth muscle. Examination of the kidney showed complete dysplasia with multifocal xanthogranulomatous inflammation.

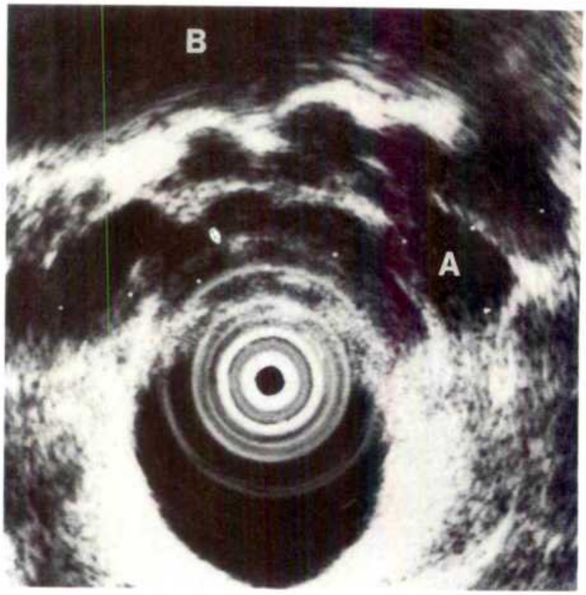

**Fig. 1** Transrectal ultrasonic examination of cystically dilated seminal vesicle (A) behind the bladder (**B**).

## Comment

True ureteric valves contain all layers of the ureter (epithelium, lamina propria and smooth muscle) except adventitia and should be distinguished from folds in the ureter which do not contain smooth muscle. The subject of ureteric valves was recently reviewed by Sant *et al.* (1985), who found a high incidence of associated genitourinary anomalies, particularly duplication. Neither of the ureters containing valves described was ectopic. A ureteric valve associated with renal dysplasia was reported by Pourmand *et al.* (1988). This ureter was also orthotopic. An ectopic ureter entering the seminal vesicle and associated with renal dysplasia was described by Gordon and Hessler (1972) but this ureter contained no valves.

The aetiology of ureteric valve formation is unknown. In the upper ureter, multiple transverse folds occur during normal fetal development but normally disappear during growth. Their persistence could be the source of some ureteric valves found after birth.

A dysplastic kidney might possibly contribute to the persistence of these valves. Renal dysplasia can also be the result of early obstruction during fetal life. Thus it is not clear whether renal dysplasia is the result or the cause of obstructing ureteric valves. Since most cases of ureteric valves are not associated with renal dysplasia but rather with hydrone-

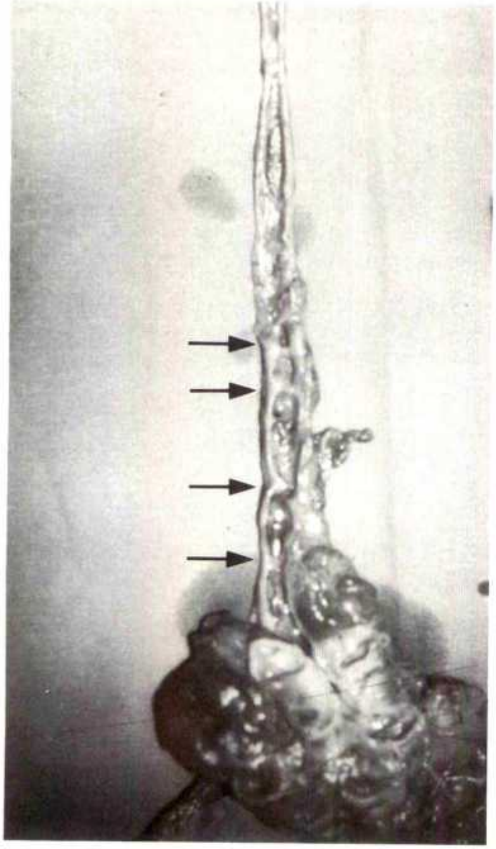

Fig. 2 The ureter has been longitudinally opened and shows several valves (arrows).

phrosis, we believe that the condition of the kidney is the result of the obstructing valves. The earlier in fetal life obstruction occurs, the more likely is dysplasia rather than hydronephrosis to result. The high incidence of other genitourinary anomalies cannot be explained by the theory of persisting fetal folds. Therefore, abnormal ureteric embryogenesis would seem to offer a better explanation for the formation of ureteric valves in the ureter, together with duplication or ectopy.

## Acknowledgements

We thank Dr H. Crispin for help in translating the manuscript and Mrs Ann Jeuris for secretarial assistance.

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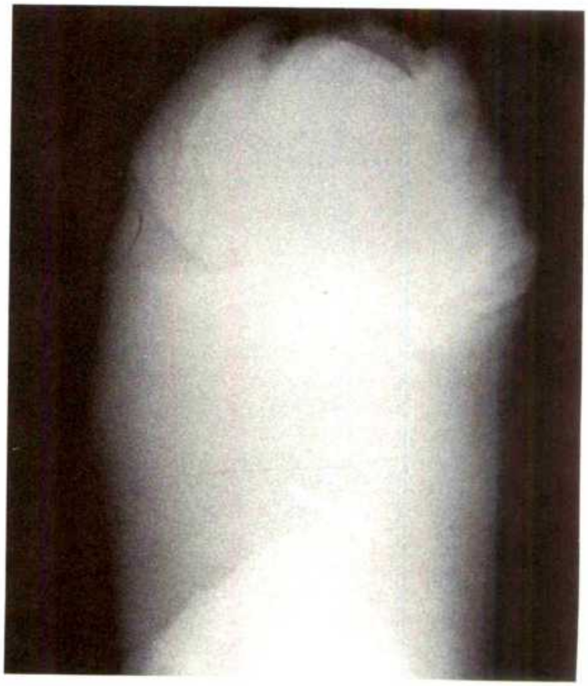
# Iatrogenic Penile Foreign Body

S. D. MARK and J. M. GRAY, *Department of Urology, Waikato Hospital, Hamilton, New Zealand*

## Case Report

A 67-year-old man presented with a history of a needle embedded in his penis. He was self-administering intracorporeal papaverine for erectile dysfunction. Immediately prior to injecting he had dropped the syringe and bent the needle. He subsequently straightened the needle, penetrated the skin and injected. The papaverine leaked around the needle and upon withdrawal the needle was missing. On palpation the needle tip could be felt in the penis.

X-ray revealed the needle tip embedded in his penis (Fig.). The needle was removed under local anaesthesia.



### Comment

Injection at home of vasoactive pharmacotherapy for the treatment of impotence is becoming more common. Short-term complications include priapism, penile nodules, bruising, urethral injections, *etc* (Sidi, 1988; Levine *et al.*, 1989).

This is the first reported case of a retained needle in the penis following self-injection of papaverine. The cost of each disposable needle (Termuo disposable 27G) to the patient is 8 ¢. Prevention of this complication is attained by advising patients to discard contaminated or bent needles prior to injection.

### Acknowledgment

We thank Miss Fiona Middleton for secretarial assistance.

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## Acute Disseminated Melioidosis Presenting as Acute Retention of Urine

T. L. QUE, Y. F. CHAN and S. Y. LAM, *Clinical Pathology Unit, Princess Margaret Hospital, Hong Kong*

### Case Report

A 53-year-old Chinese man was admitted with acute retention of urine after taking anti-tussive mixture for 1 week. He had no history of diabetes mellitus or prostatism. He was febrile on admission. Both physical examination and chest X-ray showed severe bilateral chest infection. A Foley catheter was inserted and more than 1000 ml of urine drained. He was also found to have hyperglycaemia and ketonuria. The patient died 6 h after admission despite antibiotics and insulin treatment. Blood culture taken on admission showed growth of *Pseudomonas pseudomallei*. Urine culture was negative. On necropsy multiple abscesses were found in the prostate, kidneys, liver, spleen and lungs. Section of the prostate showed numerous suppurative foci with destruction of the normal glandular pattern (Fig.). Gram stained sections of the abscesses revealed abundant Gram-negative rods admixed with the pus cells.

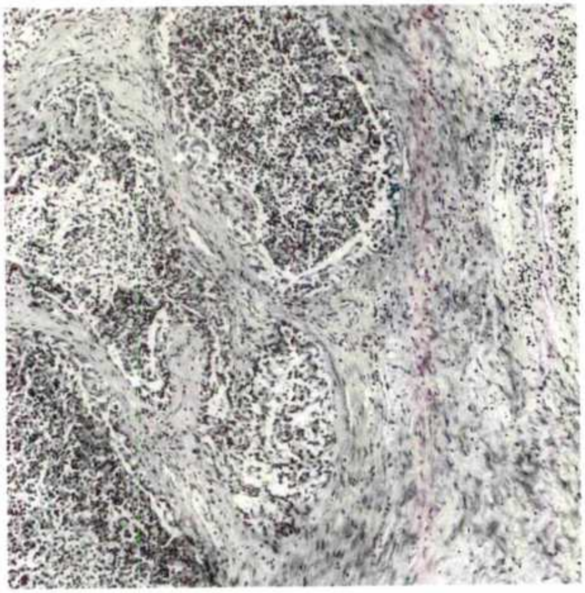

**Fig.** The prostate shows multiple large suppurative foci with destruction of glands. (H and E × 110).

### Comment

*Pseudomonas pseudomallei* infection or melioidosis is endemic in South-east Asia and the bacterium is mainly found in the soil and water. The routes of infection are inhalation, ingestion and minor trauma. Relatively few cases of melioidosis have been reported in Hong Kong, yet there is evidence that the actual incidence is likely to be much higher (So *et al.*, 1987). The infection usually presents as pulmonary infection or septicaemia, but other organs may also be involved, including liver, spleen and kidneys, either as solitary focus or as disseminated abscesses. On necropsy, the findings are usually non-specific, with abscess formation in multiple viscera. On microscopy abundant Gram-negative bacilli can often be found within the abscesses.

Our case is of interest in that the patient presented with acute urinary retention, obviously due to the acutely inflamed and enlarged prostate causing urinary obstruction. Review of the literature showed that melioidosis not uncommonly involved the upper urinary tract, but prostatic involvement causing urinary obstruction is very rare.

Acute melioidosis is rapidly fatal and has a high mortality rate of up to 90%. Unfortunately a correct diagnosis is difficult clinically and there is no reliable rapid bacteriological confirmation. The organism is not sensitive to the commonly used antibiotics such as ampicillin, first and second generation cephalosporins, aminoglycosides and the new quinolone derivatives. Tetracycline, chloramphenicol and co-trimoxazole are now the drugs of choice but the response is slow. Recent *in vitro* studies have shown that newer antibiotics such as amoxycillin/clavulanate, ceftazidime, ceftriazone, cefotaxime, piperacillin and imipenem may be useful (Chau *et al.*, 1986). A high index of suspicion and appropriate antibiotic treatment are mandatory to improve the chance of survival in these patients (Patamasucon *et al.*, 1982).

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*British Journal of Urology* (1991), 67, 558

# Notices

## British Association of Urological Surgeons

**President:** R. E. Williams, MD, ChM, FRCS, FRCSE

*Annual Meeting: Glasgow. 25–28 June 1991*

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

## Edinburgh Urological Festival

*Edinburgh. 21–23 August 1991*

Further particulars from: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Edinburgh EH4 2XU.

## Shackman Travelling Fellowship 1992

Applications are invited from Medical Practitioners registered in the United Kingdom who are either trainees in Urology or Organ Transplantation or Consultant Urological Surgeons or Consultant Surgeons with a major commitment to transplantation of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1991.

Further particulars and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

*British Journal of Urology* (1991), 67, 559–560

# Diary

1991

| | |
|---|---|
| May 10–12 | XI Athenian Days of Urology 1991, Athens, Greece. Contact: Professor C. Dimopoulos, University of Athens, Laiko Hospital, Goudi-Athens, Greece. |
| May 17 | Scottish Task Force on Incontinence. Annual Meeting, Walton Conference Centre, Southern General Hospital, Glasgow. Contact: Sister Lynn Cherry, Incontinence Resource Centre, Southern General Hospital, Glasgow. Tel. 041-425 1117. |
| May 25–26 | Fifty-sixth Congress of the Societe Belge d'Urologie, Brussels, Belgium. Contact: F. F. Wart, C.H.U.–I.M.C.A.G., Division of Urology, Bd Zoe Drion, 1, B.6.000 Charleroi–Belgium. |
| May 30–31 | Surgical Andrology, St Bartholomew's Hospital, London. Contact: BAUS Office. |
| June 2–6 | American Urological Association, Metro Toronto Convention Centre, Toronto, Canada. |
| June 7–8 | Fourth Pediatric Surgery Research Workshop, Berlin, Germany. Contact: Dr F. Schier, Pediatric Surgery, Univ.-Klinikum Steglitz, Hindernburgdamm 30, 1000 Berlin 45, Germany. Tel: (0 30) 7 98 41 81/29 09. |
| June 12–15 | Congress of the Portuguese Association of Urology. Funchal, Madeira Island. Contact: Dr Manuel Mendes Silva, Rua Consiglieri Pedrosa, 123, 2745 Queluz, Portugal. Tel: (351-1) 4354044/9. |
| une 16–20 | Canadian Urological Association Annual Meeting, Ottowa. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6. |
| June 17–22 | Diploma Course Revision Block. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |
| June 18–22 | Tenth World Congress for Sexology, Amsterdam, The Netherlands. Contact: Congress Secretariat, 10th World Congress for Sexology, c/o RAI Organisatie Bureau Amsterdam bv, Europaplein 12, 1078 GZ Amsterdam, The Netherlands. |
| June 19–23 | First World Congress of Medical Polonia, Częstochowa, Poland. Contact: Dr Zenon Rudzki, Secretary General, First World Congress of Medical Polonia, Dr Rydygier's Surgical Hospital, U1, Mirowska 25, 42-200 Częstochowa, Poland. |
| June 25–28 | BAUS Annual Meeting, Scottish Exhibition and Conference Centre, Glasgow. Contact: BAUS office. |
| July 2–3 | Diploma Course Examination. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115. |

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| August 21–23 | Edinburgh Urological Festival. Contact: Urological Festival Secretary, Department of Surgery/Urology, Western General Hospital, Crewe Rd, Edinburgh EH4 2XU. |
| August 25–31 | First Urology Summer Forum, Oosterbeek. Contact: Secretariat Organization, PO Box 226, 3830 AE LEUSDEN, The Netherlands. |
| September 1–6 | 6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96. |
| September 4–7 | Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllői ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016. |
| September 16–19 | Second Beijing International Symposium on Recent Advances in Urology, Beijing, China. Contact: Gu Fang-liu, Institute of Urology, Beijing Medical University, 1 Da Hong Luo Chang, West District, Beijing 100034, China. |
| September 26–27 | Annual Paediatric Urology Course, Selwyn College, Cambridge. Contact: Mr R H Whitaker, Dept. of Urology, Addenbrooke's Hospital, Cambridge. Tel: 0223 216344. |
| October 3–5 | Annual Meeting of Swiss Society of Urology, Geneva, Switzerland. Contact: Prof. Dr D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich, Switzerland. |
| October 4–5 | Autumn Meeting, Royal Surrey County Hospital, Guildford. Contact: BAUS Office. |
| October 9–12 | 1st International Congress, Dutch Urological Association (NVU), Rotterdam. Contact: NVU/PACIOU Congress Secretariat, Department of Urology, Erasmus University Rotterdam/Academic Hospital Dijkzigt, P.O. Box 1738, 3000 DR Rotterdam. The Netherlands. |
| October 10–12 | International Continence Society, 21st Annual Meeting, Hannover. Contact: Guu Kramer, Chairman ICS, Department of Urology, Hannover Medical School, P.O Box 610180, 3000 Hannover 61, Germany. |
| October 18–19 | Surgical Treatment of Prostatic Cancer: Comparison of Techniques. Milan, Italy. Contact: Dr F. Gaboardi, Divisione di Urologia, Ospedale Fatebenefratelli ed Oftalmico, C.so Porta Nuova 23, 20121 Milan, Italy. Tel. 0039-2-636443. |
| October 20–<br>November 4 | Royal College of Surgeons of England Joint Meetings in Pakistan and India. Contact: Craig Duncan, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London, WC2A 3PN. |

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| January 10 | Final date for submission of abstracts for the 1992 BAUS Annual Meeting. |
| May 6–8 | 8th International Symposium on Radionuclides in Nephrourology, The Grosvenor Hotel, Chester, England. Contact: Mr P H O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport, SK2 7JE. |
| May 10–14 | American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC. |